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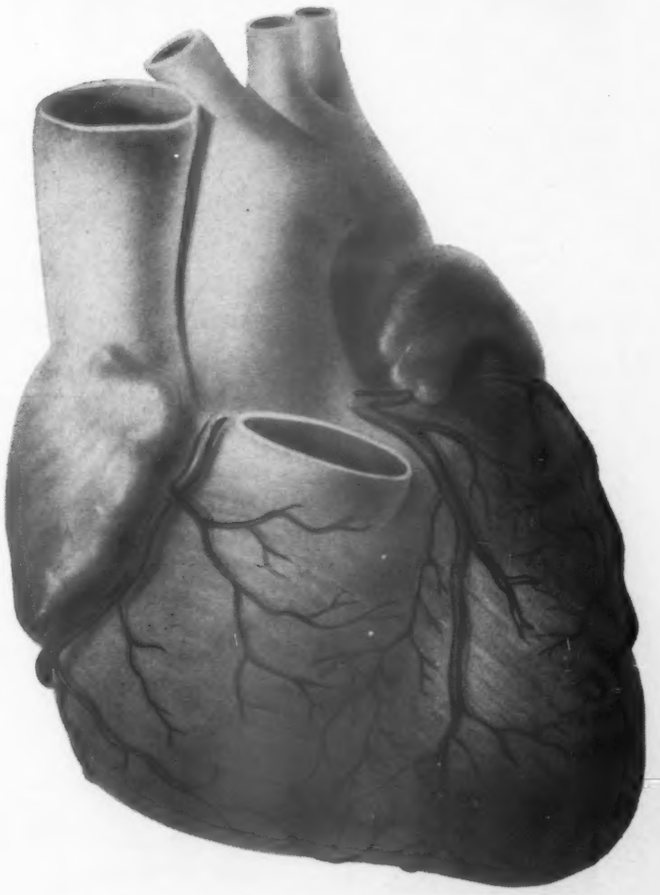

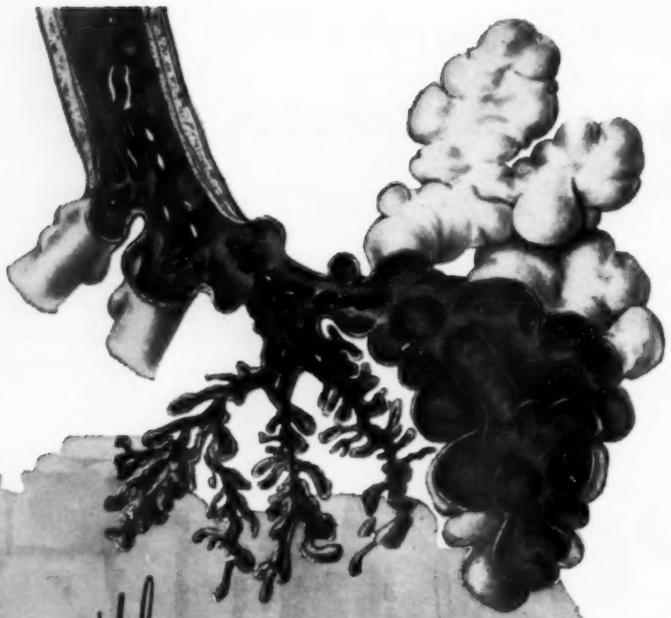

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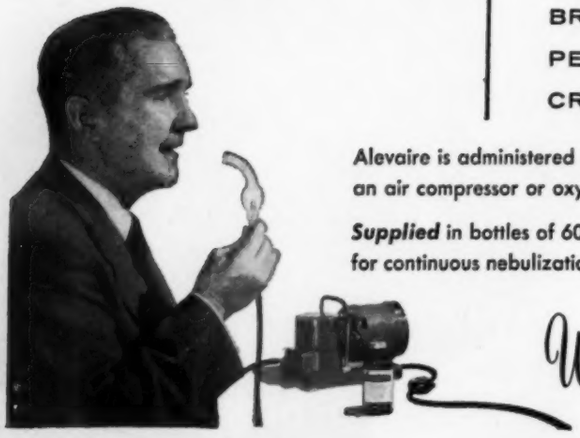

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The Identification and Quantification of Left-to-Right Circulatory Shunts. A New Diagnostic Method Utilizing the Inhalation of a Radioactive Gas, Kr^{85}
RICHARD J. SANDERS AND ANDREW G. MORROW 508

Improved technics of cardiac surgery have made it imperative to increase the accuracy of diagnosis of left-to-right circulatory shunts. The authors present a new diagnostic method utilizing a radioactive gas, Krypton^{85}, and compare the results obtained with the previously described nitrous oxide technic, and the more conventional oxygen method. Kr^{85} and N_2O methods are both superior to the older oxygen technic as regards accuracy of diagnosis as well as quantification of shunt flow. While the N_2O test is as accurate as the Kr^{85} test, the rapidity and ease of determination of the latter make this newer method a significant addition to preoperative cardiac evaluation.

Pulmonary Artery Stenosis . . . . HAROLD A. SHAFTER and HARRY A. BLISS 517

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Differential Pulmonary Artery Occlusion in Patients with Chronic Pulmonary Disease
B. L. CHARMS, B. L. BROFMAN AND A. ADICOFF 527

The technic of temporary unilateral pulmonary artery balloon occlusion was employed in the investigation of five cases of pulmonary disease. Significant reduction in venous admixture (with rise in arterial oxygen content and pressure) after occlusion of the pulmonary artery branch to an involved lung suggested that the lesion was primarily responsible for this increased venous admixture. Failure to obtain improvement in venous admixture indicated diffuse disease of the lung and contraindicated resection of the lesion. The five cases presented illustrate the use of this technic in evaluating patients for surgery.

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Source: Skilboe, B.: Am. J. Clin. Path. *30*:252, 1958.

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(1) Beckman, H.: Drugs: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 425.
(2) Biliary Tract Diseases, M. Times *85*:1081, 1957.

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Intracardiac Electrocardiography in Man
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The technic of intracardiac electrocardiography has been known for some time but has not been regularly employed as an adjunct to the usual cardiac catheterization procedures. The present authors point out several advantages of the method in this connection, including more precise localization of the catheter tip, warning of impingement upon the endocardium or entry into the coronary sinus, and facilitation of diagnosis of conduction abnormalities which may not be apparent in surface leads.

Incidence and Significance of Abnormal Hemoglobins. Report of a Series of 1,000 Hospitalized Negro Veterans
RALPH M. MYERSON, ESTHER HARRISON AND HERBERT W. LOHMULLER 543

In a survey of the incidence of hemoglobinopathies in 1,000 hospitalized Negro veterans, 10.6 per cent of the electrophoretograms indicated one or another abnormality, distributed as follows: AS, 8.5 per cent; SS, 0.4 per cent; SC, 0.1 per cent; AC, 2.2 per cent; CC, 0.1 per cent; other anomalies, 0.2 per cent. The occurrence of renal infarcts with gross hematuria in S- and C-trait is again emphasized.

The Role of Splenectomy in the Management of Acquired Autoimmune Hemolytic Anemia Complicating Systemic Lupus Erythematosus
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Having previously stated the case against splenectomy for autoimmune hemolytic anemia in systemic lupus erythematosus (*Am. J. Med.*, 21: 560, 1956), it seems appropriate now to put the case for it. Three such patients are described and in each instance it is concluded that splenectomy was beneficial in respect to the anemia and not detrimental in respect to the underlying disease. Granted that the follow-up in these cases was short, and the results of splenectomy only a qualified success, the authors are able to lend support to their views on the basis of their own experience and that of others. Until more data are available, opinion for or against splenectomy in this situation should not be arbitrary.

Infectious Hepatitis in Clearfield County, Pennsylvania. I. A Probable Water-Borne Epidemic
JAMES W. MOSLEY, W. D. SCHRACK, JR., THEODORE W. DENSHAM AND L. D. MATTER 555

This is an interesting example of a detailed epidemiologic analysis of an epidemic of infectious hepatitis. In this instance, as in some previously reported, the virus was water-borne and the contaminating source could be traced with a high degree of probability.

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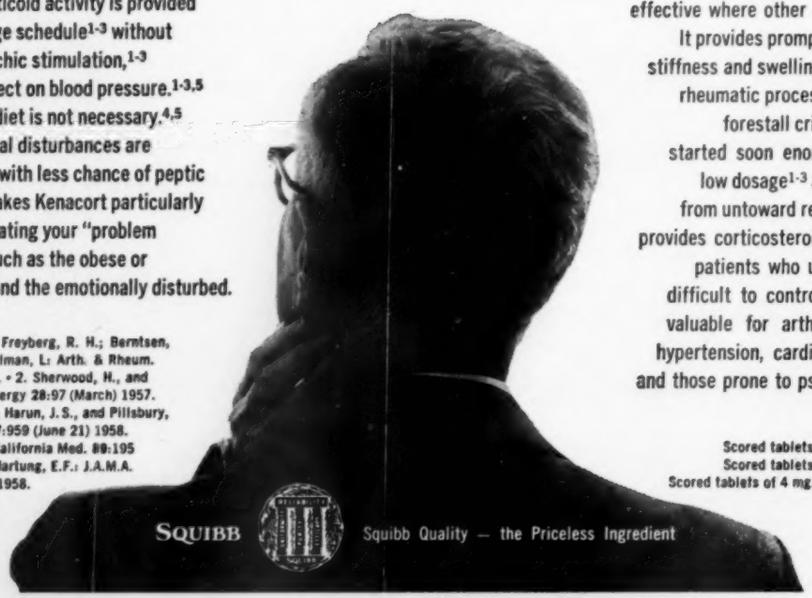

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The Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia . . . . . E. D. ACHESON 569

Dr. Acheson has put together a comprehensive and well balanced summation of present knowledge concerning the curious disorder of unknown (viral?) etiology most commonly known as Iceland disease, which has been confused with but is certainly distinct from poliomyelitis. It usually occurs in epidemic form, but may be sporadic, particularly involving hospital personnel, notably nurses. The clinical course in severe cases characteristically begins fairly acutely with headache, gastrointestinal or respiratory complaints and muscle aches and pains; fever is absent or mild, cerebrospinal fluid and other laboratory examinations are essentially normal. An unusual type of paresis then develops, without the classic signs of lower motor neurone or pyramidal tract involvement, accompanied by paresthesias and sometimes by a variety of involuntary muscle movements and spasms. The mortality rate is nil, but full recovery may be delayed by exacerbations and prolonged fatiguability, depression and emotional disturbances sometimes suggestive of hysterical overlay. Certainly an interesting disease here well delineated.

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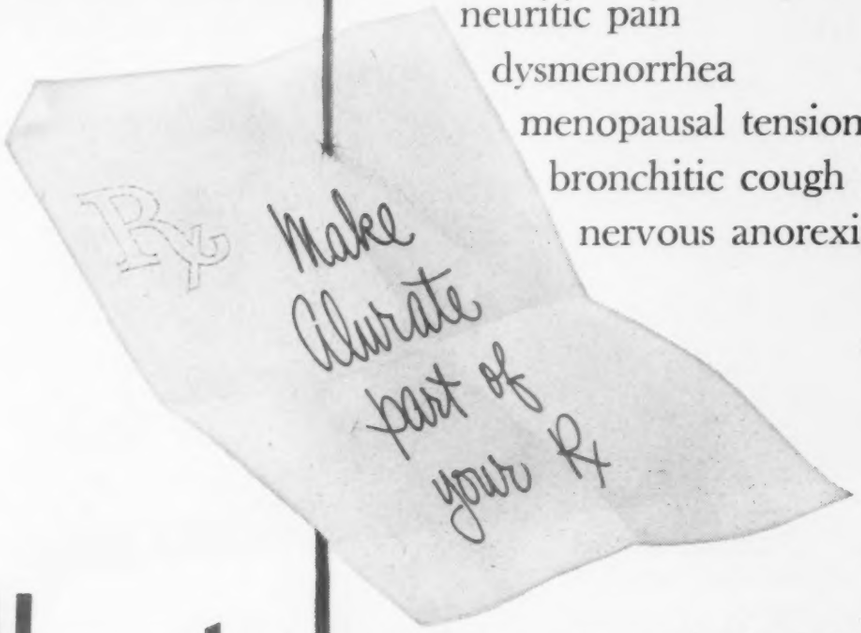

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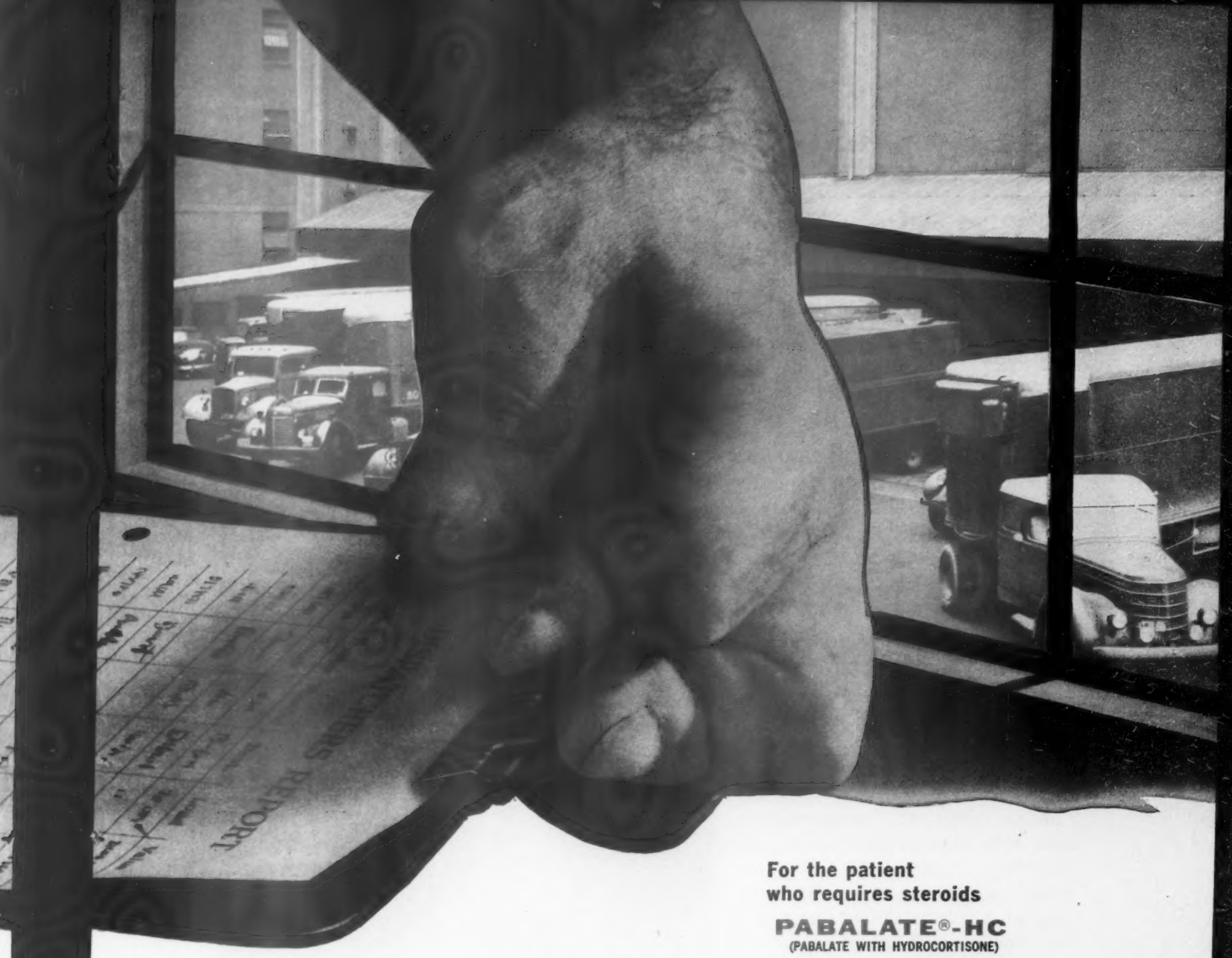

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*H. D. Green and H. H. DuBose, Circulation, 10:374, 1954.

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1. Batterman, R. C.; Grossman, A. J.; Mouratoff, G. J., and Leifer, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit, Annual Meeting of AMA, San Francisco, June 23-27, 1958.
2. Grossman, A. J.; Batterman, R. C., and Leifer, P.: Fed. Proc. *17*:373 (March) 1958.

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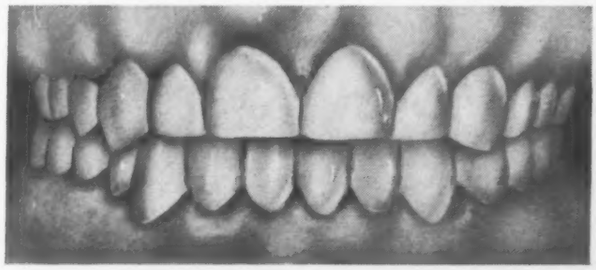

Dryness of mouth; hyperemic swollen gums and mucous membranes; burning sensations in lips, tongue and palate, and loss of filiform papillae.
Source: Sindoni, A., Jr.: Dental Clin. North America 2:459 (July) 1958.

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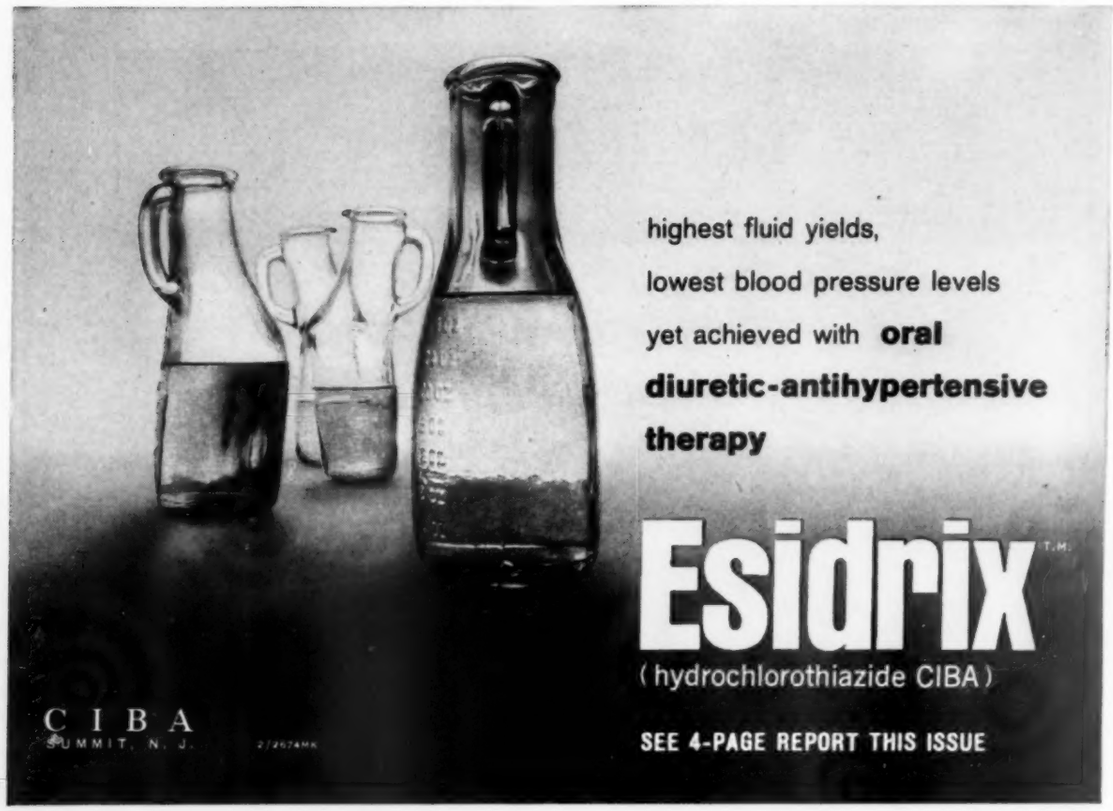

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References:

1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychiat. 115:250, Sept. 1958.

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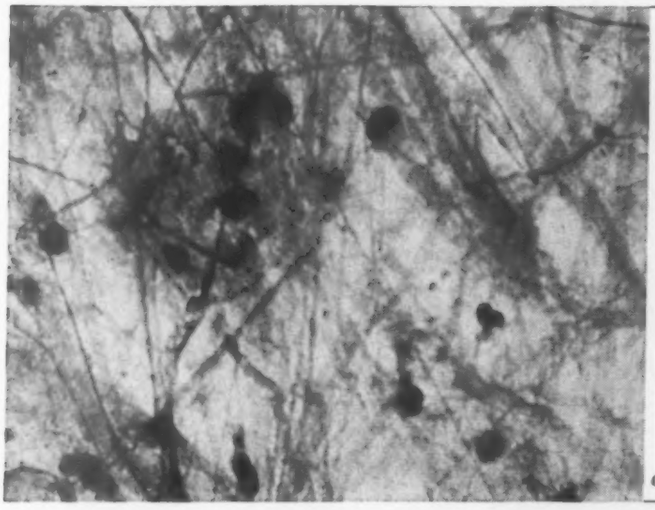

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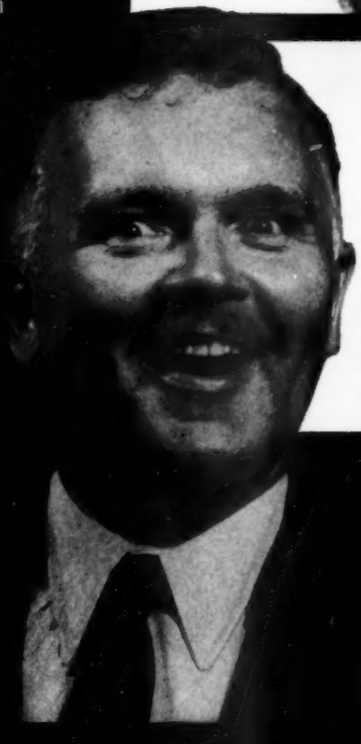

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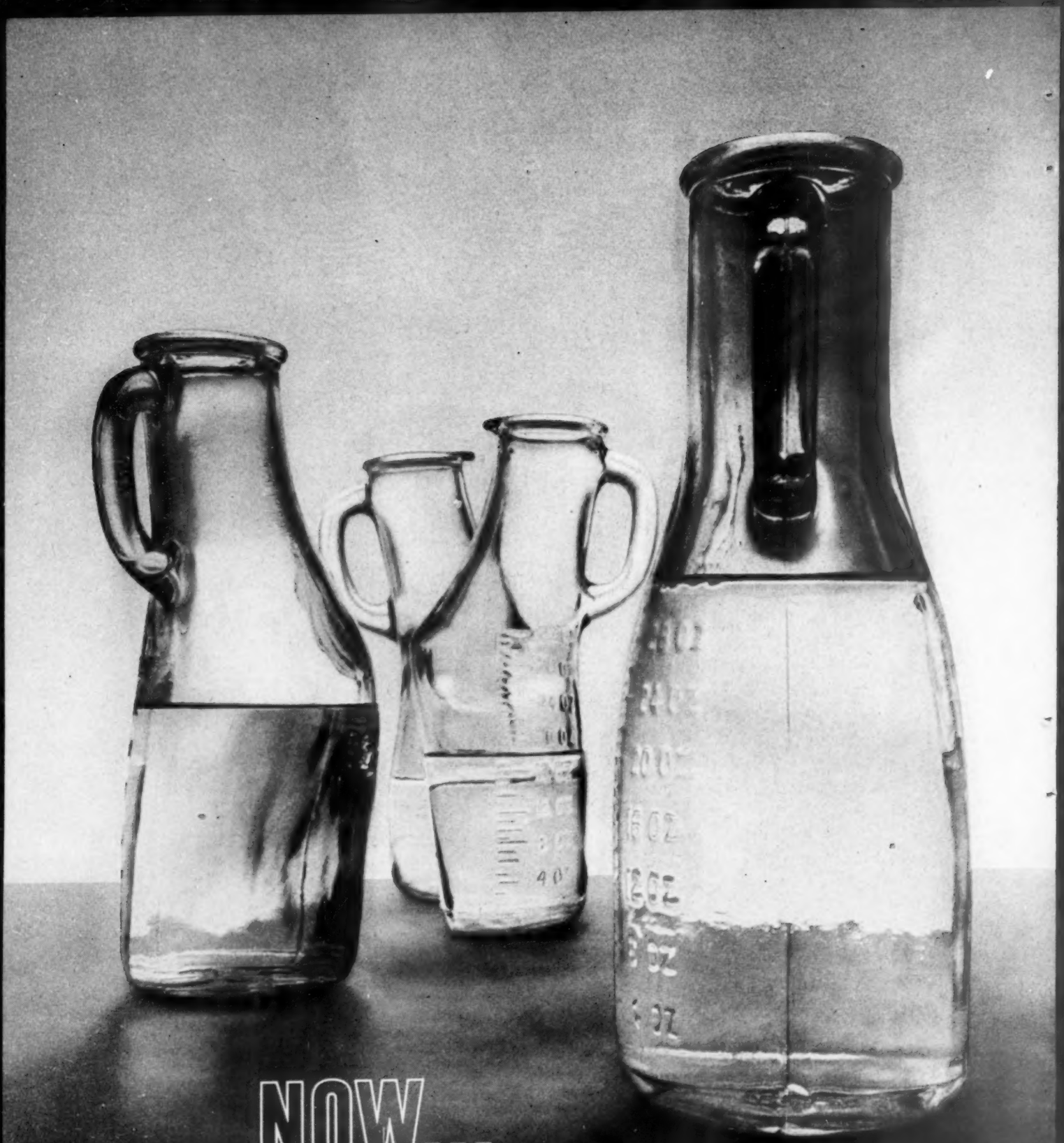

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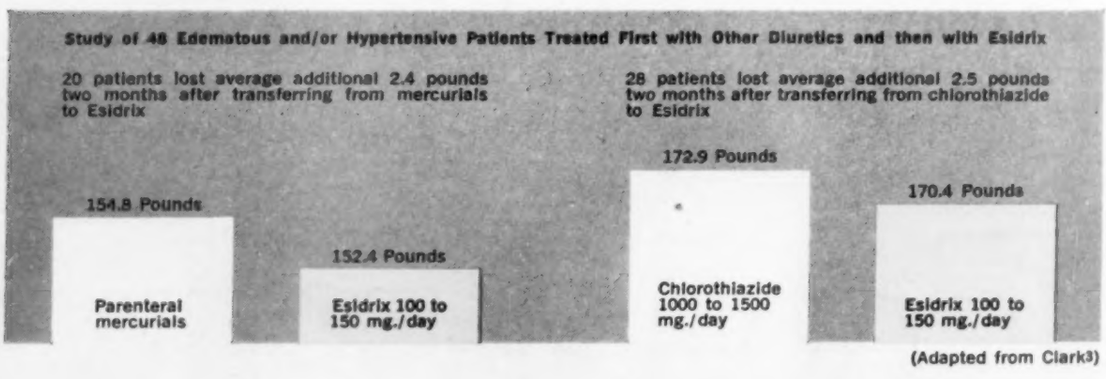
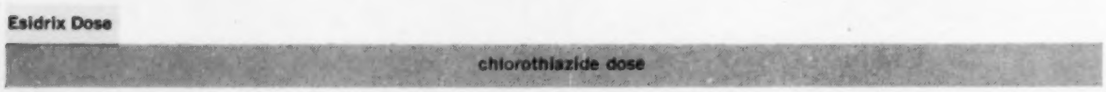
Esidrix: 10 to 15 times more active than chlorothiazide in edema and hypertension

Esidrix relieves edema in many patients refractory to other diuretics: Studies reveal that certain patients unresponsive or refractory to mercurials and chlorothiazide respond readily to Esidrix. Brest and Likoff[1] observed that 9 of 12 patients with congestive heart failure—who failed to respond to other diuretics—were completely controlled with Esidrix. Esidrix appears to have clinical value even after the patient has developed partial tolerance to chlorothiazide, and may be found useful in cases of sensitivity to chlorothiazide.[2]

Therapy with Esidrix often results in more weight loss than with other diuretics: In a study[3] of 48 patients with edema and/or hypertension, who were treated originally with chlorothiazide or with mercurial diuretics, substitution of Esidrix at a dose of 100 to 150 mg./day resulted in additional average weight loss of 2.4 to 2.5 pounds.


Study of 48 Edematous and/or Hypertensive Patients Treated First with Other Diuretics and then with Esidrix
20 patients lost average additional 2.4 pounds two months after transferring from mercurials to Esidrix
28 patients lost average additional 2.5 pounds two months after transferring from chlorothiazide to Esidrix
154.8 Pounds
152.4 Pounds
172.9 Pounds
170.4 Pounds
Parenteral mercurials
Esidrix 100 to 150 mg./day
Chlorothiazide 1000 to 1500 mg./day
Esidrix 100 to 150 mg./day

(Adapted from Clark3)



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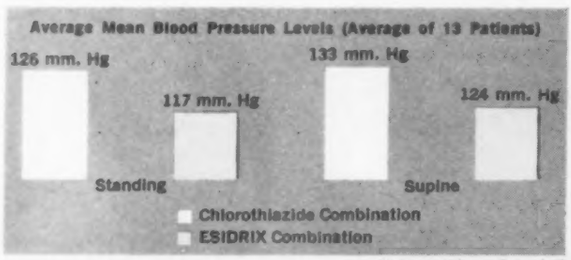
Esidrix T.M.

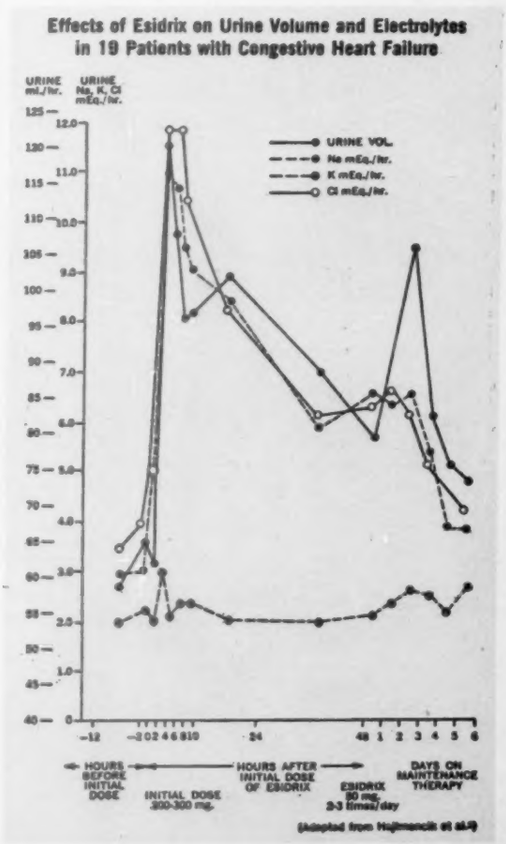
(hydrochlorothiazide CIBA)

Produces greater average reduction in blood pressure: Eleven of 13 hypertensive patients[4] were treated initially with a chlorothiazide-mecamylamine-reserpine combination (10 patients had 1000 mg. and 1 patient 500 mg. chlorothiazide daily); 1 patient had been treated with hydralazine and 1 had no previous medication. Nine were then transferred to an Esidrix-mecamylamine-reserpine combination and 4 to an Esidrix-reserpine combination for periods of 3 to 7 weeks (12 patients had 100 mg. and 1 patient 50 mg. Esidrix daily). Average mean blood pressure levels were recorded in the standing and supine positions. As shown in graph below, left, there was a further drop in blood pressure after patients were transferred to Esidrix.



(Adapted from Dennis[4])

Exceptional safety... reduced likelihood of electrolyte imbalance: While Esidrix markedly increases sodium and chloride excretion, it has far less effect on excretion of potassium (see chart at right) and bicarbonate. Hence, there is little likelihood of disturbing electrolyte balance when recommended procedures are followed.


Effects of Esidrix on Urine Volume and Electrolytes in 19 Patients with Congestive Heart Failure
URINE ml./hr.
URINE Na, K, Cl mEq./hr.
URINE VOL.
Na mEq./hr.
K mEq./hr.
Cl mEq./hr.
HOURS BEFORE INITIAL DOSE
INITIAL DOSE 300-300 mg.
HOURS AFTER INITIAL DOSE OF ESIDRIX
ESIDRIX 50 mg. 2-3 times/day
DAYS ON MAINTENANCE THERAPY

(Adapted from Hollmerich et al.[5])

DOSAGE: Esidrix is administered orally in an average dose of 75 to 100 mg. daily, with a range of 25 to 200 mg. A single dose may be given in the morning or tablets may be administered 2 or 3 times a day.

SUPPLIED: *Tablets,* 25 mg. (pink, scored); bottles of 100 and 1000. *Tablets,* 50 mg. (yellow, scored); bottles of 100 and 1000.

in alcoholism[1,2]

ACUTE EMERGENCIES — a single intramuscular injection of 50 mg. (2 cc.) Vistaril Parenteral Solution is usually sufficient to calm the patient and initiate sound sleep. Vistaril is exceptionally well tolerated. Antiemetic action and absence of respiratory depression are among valuable assets reported.

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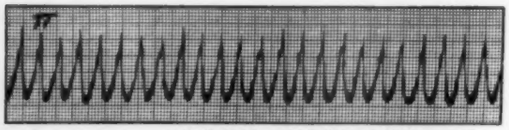

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in arrhythmias[3,4]

Many types of cardiac arrhythmias respond promptly to oral, intramuscular or intravenous Vistaril therapy. Vistaril is particularly effective in ventricular extrasystoles, paroxysmal tachycardias (both auricular and ventricular), and ventricular extrasystoles complicating auricular fibrillation. The following dosage regimen is recommended:

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ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY: *Vistaril Capsules, 25 mg., 50 mg. and 100 mg. Vistaril Parenteral Solution, 10 cc. vials, and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydroxyzine hydrochloride.*

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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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effective by itself in some patients—always as background medication in any antihypertensive regimen.

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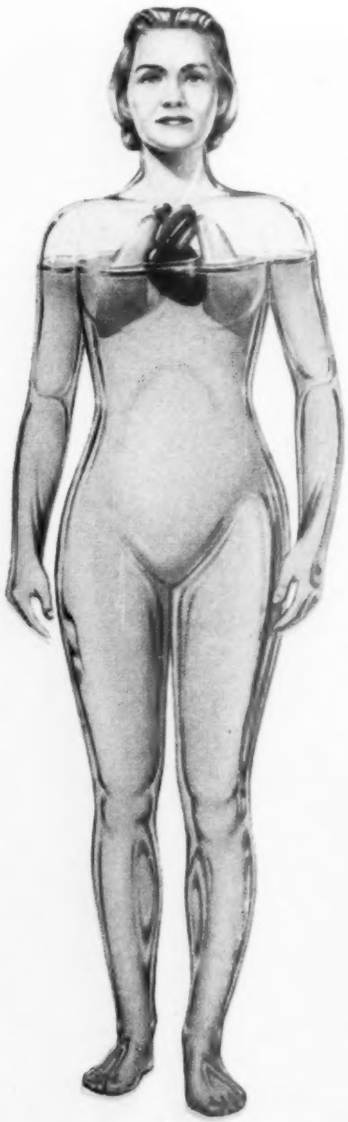

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- highly-active derivative of chlorothiazide
- similar qualitatively to chlorothiazide but 10 to 12 times more potent
- loss of potassium is clinically insignificant in the great majority of patients on normal diets

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- provides background therapy in any antihypertensive regimen (by itself, HYDRO**DIURIL** adequately controls hypertension in some patients)
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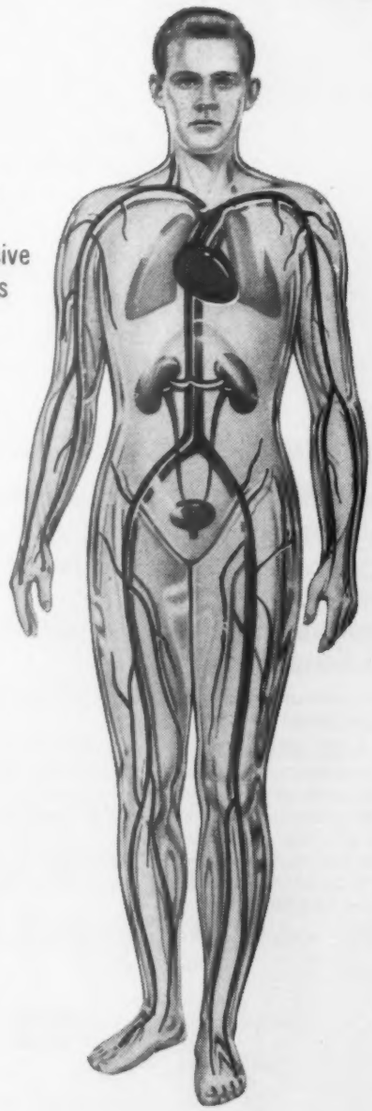
- reduces dosage requirements for other agents, often with concomitant reduction in their distressing side effects
- smooths out blood pressure fluctuations



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In **EDEMA:** one to two 50 mg. tablets HYDRODIURIL once or twice a day

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SUPPLIED as 25 mg. and 50 mg. scored tablets, in bottles of 100 and 1000.

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Additional information on HYDRODIURIL is available on request.

BIBLIOGRAPHY:

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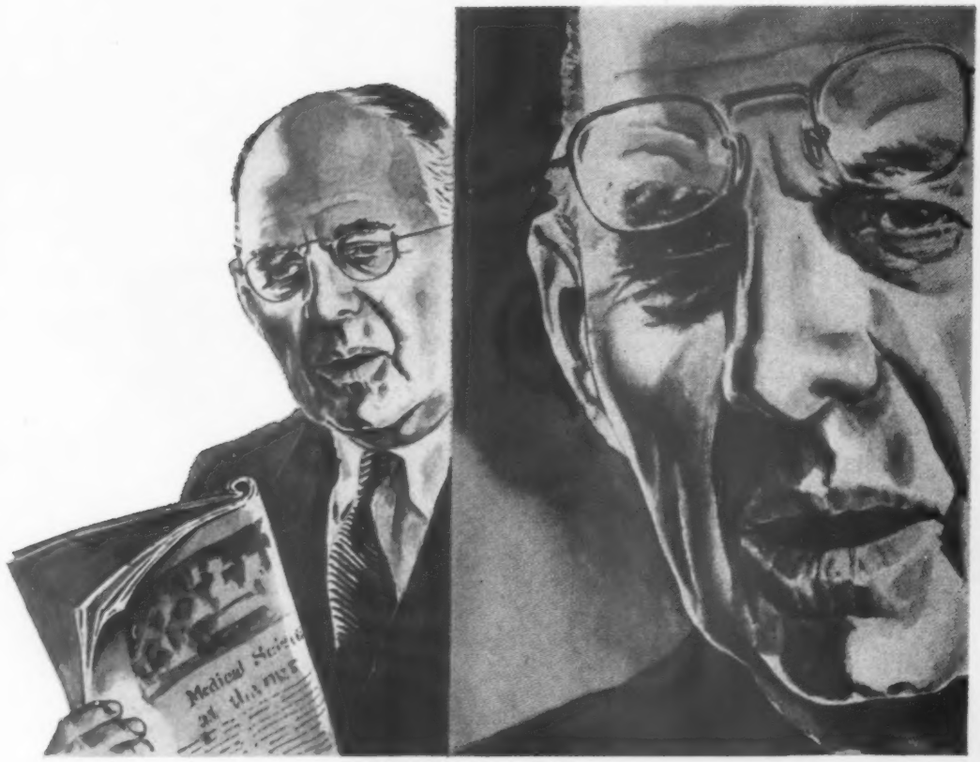

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Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide, and Butabarbital, Wyeth

*Sedative and Anticholinergic

SUPPLIED: SUSPENSION, bottles of 12 fl. oz. TABLETS, bottles of 100. Each teaspoonful (5 cc.) and tablet contains 2.5 mg. of ambutonium and 8 mg. of butabarbital combined with aluminum hydroxide and magnesium hydroxide approximating 1 teaspoonful of aluminum hydroxide gel and ¼ teaspoonful of milk of magnesia. Also available: Tablets Ambutonium Bromide, 10 mg., bottles of 100.

Wyeth®

Philadelphia 1, Pa.

Combined Orinase*-insulin therapy enables you to "stabilize" a surprising percentage of "brittle" diabetics

The primary indication for Orinase remains in the stable, maturity-onset diabetic in whom Orinase usually can fully replace insulin therapy. But now a further indication has developed from the cumulative data of the past several years: many labile diabetics, who cannot be managed on Orinase alone, can benefit from the *addition* of Orinase to their insulin regimen.

A major benefit—stabilization

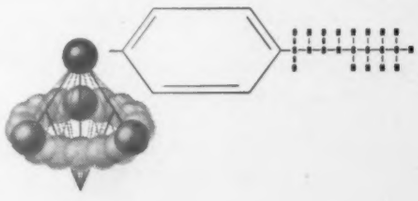
In the labile diabetic who successfully responds to joint insulin-Orinase management, the "peaks and valleys" of erratic blood sugar levels are rarely observed. The addition of Orinase greatly reduces sudden and unexpected changes... tends to "stabilize" even the "brittle" diabetic.

A major benefit—lessened insulin needs

The Orinase-stabilized labile diabetic generally requires less insulin than before the inclusion of Orinase in his regimen. This lessening of insulin dosage is particularly advantageous in the patient who is insulin-dependent, but who reacts unfavorably — whether by lipodystrophy or otherwise — to insulin.

The derived benefits—less hypoglycemia, less anxiety, greater well-being

With stabilization, the hazards of shock or coma are diminished. Like the diabetic who is responsive to Orinase alone, the labile diabetic on combined therapy need no longer walk a slender tightrope between hypo- and hyperglycemia. The patient's fears are greatly lessened ...often to be replaced by the healthier outlook characteristic of *euglycemic* Orinase management. *TRADEMARK, REG. U. S. PAT. OFF.— TOLBUTAMIDE, UPJOHN



AN EXCLUSIVE METHYL "GOVERNOR" PREVENTS HYPOGLYCEMIA . . . MAKES ORINASE A TRUE EUGLYCEMIC AGENT

Upjohn

The Upjohn Company
Kalamazoo, Michigan

PAIN Zactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation[1,2,3] in 1998 patients in diverse areas of medicine and surgery, including:

arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

- *exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action*
- *prompt, potent action—as potent as codeine*
- *documented effectiveness and safety[1,2,3]*

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

Wyeth®
Philadelphia 1, Pa.

1. Cass, L.J., et al.: J.A.M.A. *166*:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc. *234*:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.

Obedrin®

and the 60-10-70 Basic Plan

provide a rational weight control regimen

When the optimum weight is reached—the maintenance of desired eating patterns is most important. Continuing support by the physician is necessary. Here, Obedrin and the 60-10-70 Plan can be valuable aids to both the physician and patient.

FORMULA: *tablets and capsules*

Semoxydrine® HCl (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine Mononitrate	0.5 mg.
Riboflavin	1 mg.
Nicotinic Acid	5 mg.

OBEDRIN PROVIDES:

- Methamphetamine for its proven anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Bristol, Tennessee · New York · Kansas City · San Francisco THE S. E. MASSENGILL COMPANY

for effective timing...a flexible dosage form

tablets or capsules

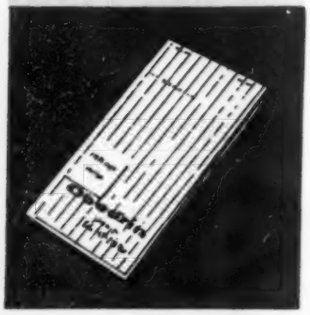
LUNCH DINNER EVENING SNACK

Obedrin tablets or capsules provide a flexible dosage form which may be prescribed to depress the appetite at peak hunger periods.

The pentobarbital content assures control of excess central nervous stimulation, and the 60-10-70 Basic Plan provides for a balanced food intake with sufficient protein and roughage.

Obedrin is available in tablet and capsule form.

Currently, mailings will be forwarded only at your request. Write for 60-10-70 menus, weight charts, and samples of Obedrin



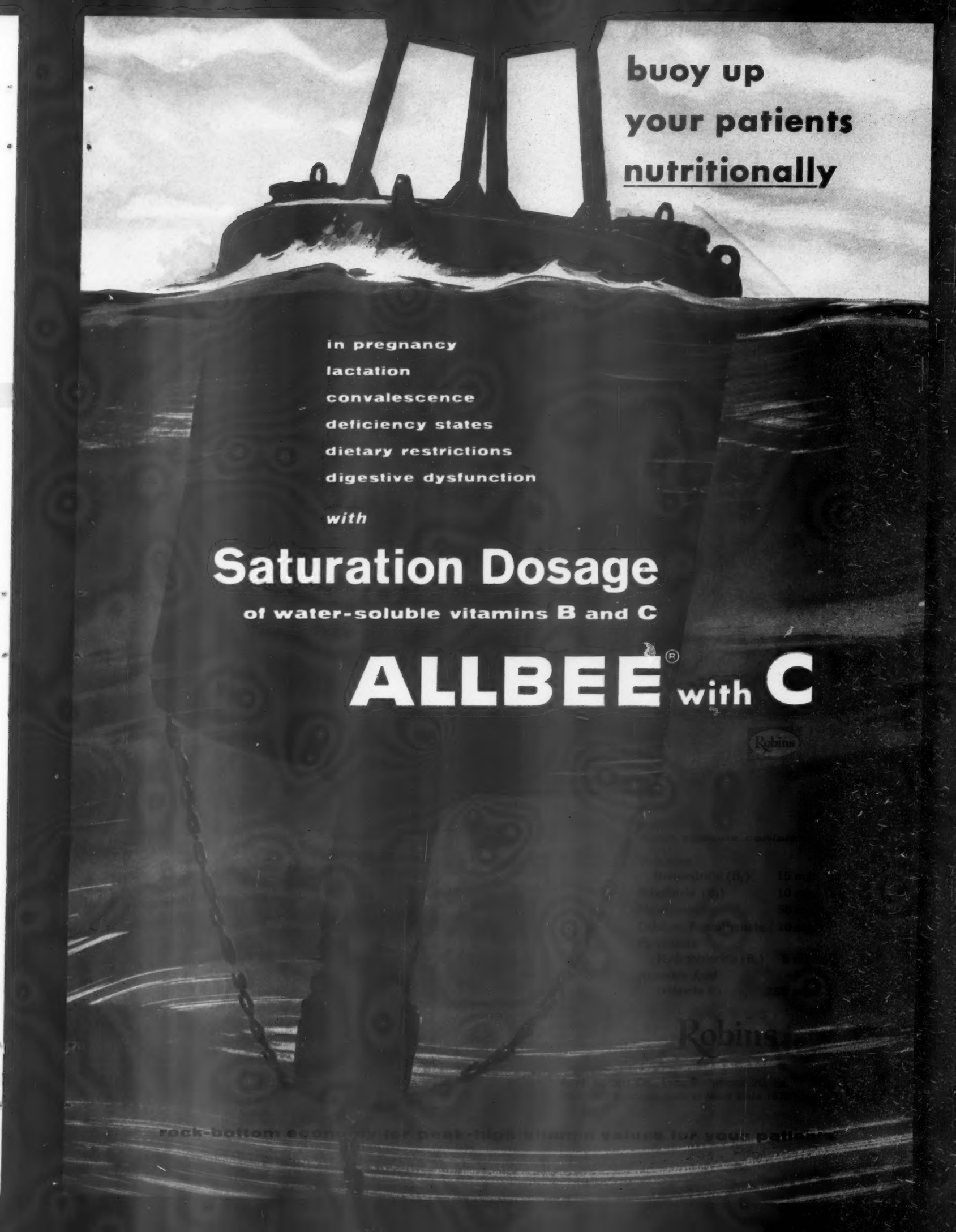
ADVANTAGES OF OBEDRIN

- An effective anorexigenic agent
- A flexible dosage form
- Minimal central nervous stimulation
- Vitamins to supplement the diet
- No hazards of impaction

Obedrin®

and the 60-10-70 Basic Plan

Bristol, Tennessee · New York · Kansas City · San Francisco **THE S. E. MASSENGILL COMPANY**


buoy up
your patients
nutritionally
in pregnancy
lactation
convalescence
deficiency states
dietary restrictions
digestive dysfunction
with
Saturation Dosage
of water-soluble vitamins B and C
ALLBEE® with C
Robins

The Menopausal Arthritic....

NEEDS STENISONE TO RELIEVE HER SYMPTOMS ...YET AVOID INSIDIOUS SIDE EFFECTS

Here is a clinical portrait of the Menopausal Arthritic and her strange new problems which, up to now, have eluded simplified therapy:

Age: 45-60. Declining gonadal function, with tendency to osteoporosis. Overlapping symptoms: flushes, palpitation, nervousness, apprehension, weakness, fatigue, arthralgias, myalgias, loss of muscle tone,[1] slight flexion contractures. An obvious candidate for corticosteroid therapy – and for its two prevalent side effects, osteoporosis (as high as 26 per cent[2]) and steroid ulcer (as high as 31 per cent.[3])

Relieve symptoms yet guard against osteoporosis and steroid ulcer with new **Stenisone®**

5 mg. *prednisone*—clinically proved anti-inflammatory steroid.[4]

20 mg. *methandriol*—proven anabolic, nitrogen-sparing steroid.[5] Also relieves menopausal symptoms.[6]

366.6 mg. *gastric protectors* (Trevidal®) to help avoid steroid ulcer.

For Menopausal Arthritics or wherever corticosteroids are useful, STENISONE is *more safely useful.*

REFERENCES: 1. Stein, I., and M. L. Beller, *Geriatrics, 14*:99, 1959. 2. Howell, D. S., and C. Ragan, *Medicine, 35*:83, 1956. 3. Kammerer, W. H., *et al., Arth. and Rheum., 1*:122, 1958. 4. Ward, L. E., *et al., Ann. Rheum. Dis., 17*:145, 1958. 5. Banghart, H. E., *Amer. Prac., 5*:964, 1954. 6. Perloff, W. H., *J. Phila. Gen. Hosp., 2*:90, 1951.

Organon ORGANON INC., ORANGE, NEW JERSEY

In Mild Depression

Deaner

p-acetamidobenzoic acid salt of 2-dimethylaminoethanol

Anti-Depressant

Do Not confuse it with tranquilizers

'Deaner' must not be confused with tranquilizing or sedative drugs which may aggravate depression. On the contrary, 'Deaner' is often used to counteract drug-induced depression.

'Deaner' is valuable as an emotional normalizer in many situations other than depression, such as behavior problems with agitation. Nor should 'Deaner' be considered an ordinary stimulant. Its gentle action differs from that of other stimulants in that it leads to increased useful energy and alertness without the undesirable side effects of the amphetamine-like drugs.

Literature and bibliography available upon request.

Deaner a totally new molecule, offers a new type of alleviation in depression, fatigue states and many other emotional disturbances. Its physiologic effectiveness as a safe central nervous system stimulant is attributed to its activity as a probable precursor to acetylcholine.

Deaner leads to better ability to concentrate, increased daytime energy, sounder sleep (with less sleep needed), and a more affable mood.

Deaner acts gently, gradually, and its effects are prolonged... without causing hyperirritability... without loss of appetite... without elevating blood pressure or heart rate... without sudden letdown on discontinuance.

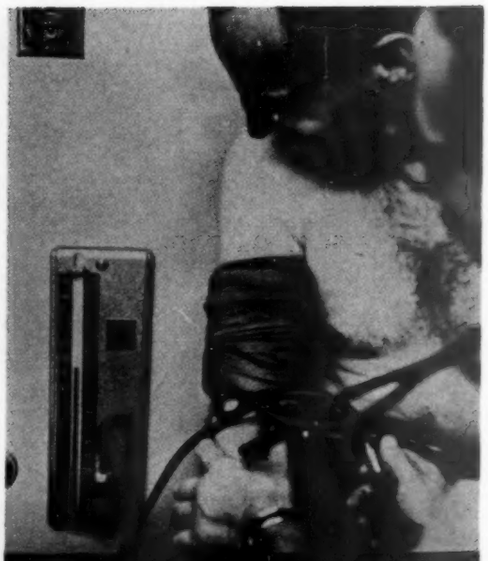
Deaner is valuable in the treatment of children, especially those whose performance is impaired by behavior problems, whose attention span is too short, and who are emotionally unstable, unpredictable, and unadaptable.

Dosage: Initially, 1 tablet (25 mg.) in the morning. Maintenance dose, 1 to 3 tablets; for children, ½ to 3 tablets. Three to four weeks of therapy may be required for maximum benefit.

Riker Northridge, California

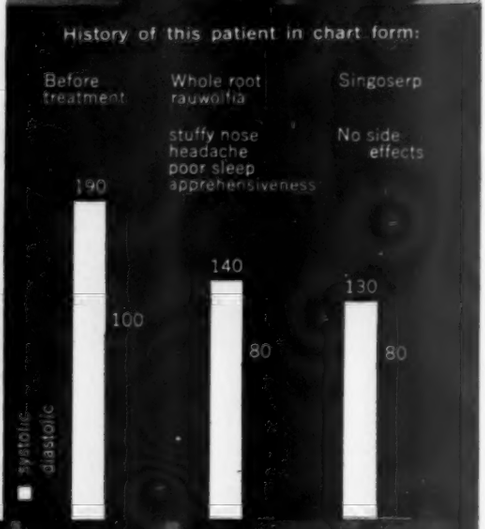
With Singoserp this patient's blood pressure was controlled for the first time without side effects

FROM THE FILES OF A PHILADELPHIA CARDIOLOGIST. PHOTOS USED WITH PERMISSION OF THE PATIENT.

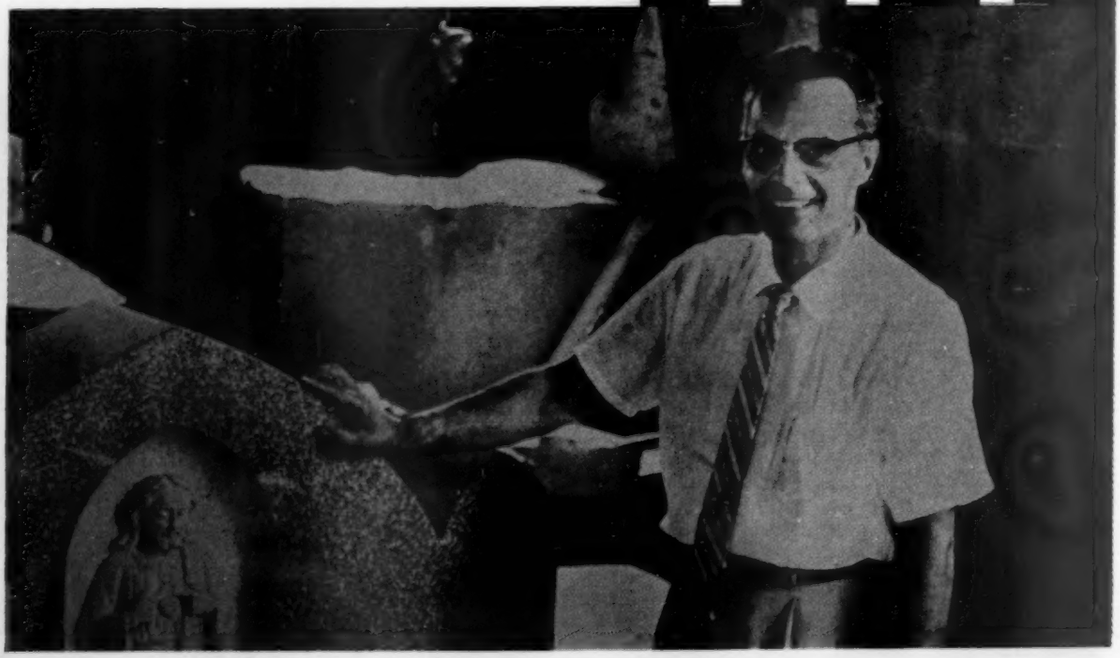


Tombstone salesman had known hypertension for 16 years; rejected by U.S. Army because of high blood pressure. Whole root rauwolfia lowered pressure satisfactorily, but patient could not tolerate side effects.

History of this patient in chart form:



Singoserp in a dosage of 0.5 mg. daily lowered his blood pressure to 130/80, produced no side effects. Patient feels well, works well, speaks of marked improvement in outlook and function.



Clinical findings in 900 patients show the selective antihypertensive action of Singoserp

IN 735 PATIENTS, BLOOD PRESSURE FELL AN AVERAGE OF 30.7 mm. Hg:

- more than half of these patients suffered from **moderate to severe hypertension**
- more than half of the cases involved hypertension of at least 6 years' standing, with **many histories of up to 20 years' duration**

THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication

Side Effect	Number	Per Cent
Lethargy	7	2.9
Headache	6	2.5
Gastrointestinal upset	3	1.2
Vertigo	2	0.8
Nasal congestion	1	0.4

DOSAGE:
In new patients: **Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from ½ to 3 tablets (0.5 to 3 mg.) daily.**

In patients taking other antihypertensive medication: **Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.**

Singoserp®
(syrosingopine CIBA)

a major improvement in rauwolfia

a major advance in antihypertensive therapy

CIBA
SUMMIT N J

2/2668MK

In hypoprothrombinemia

STOP BLEEDING BEFORE IT BEGINS

PROPHYLACTICALLY

Before delivery KONAKION prevents neonatal hemorrhage, rapidly establishes physiologic prothrombin levels in the newborn.

and

Before surgery KONAKION minimizes the risk of hemorrhage by normalizing prothrombin time, especially important in biliary procedures.

THERAPEUTICALLY

KONAKION for

- excessive hypoprothrombinemia due to anticoagulant therapy
- inadequate intake or utilization of vitamin K
- neonatal hemorrhage
- g.i. disorders with prolonged diarrhea

KONAKION—a potent synthetic vitamin K_1 with a wide margin of safety and rapid rate of absorption unequaled by other vitamin K preparations. Convenient low-dosage forms for *oral, intramuscular,* or *intravenous* administration. The parenteral form is an *exceptionally fine aqueous dispersion,* compatible with most I.V. vehicles, and packaged for economical one-time use.

NEW KONAKION®

Capsules—5 mg; Ampuls—1 mg/0.5 cc, 10 mg/1.0 cc, 25 mg/2.5 cc

brand of vitamin K_1

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

A CIBA Documentary Report

How clinicians evaluate the safety and effectiveness of RITALIN® as a psychic stimulant

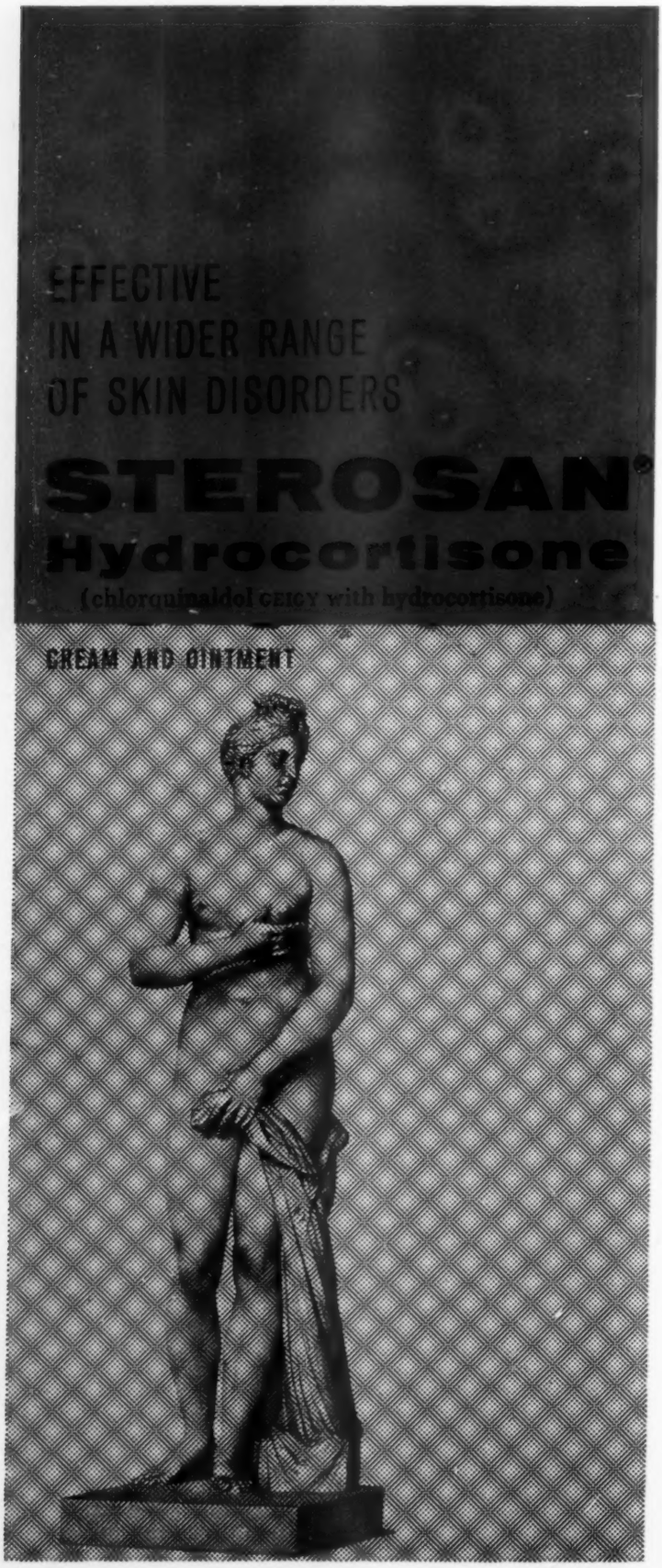
CONDITIONS TREATED	RESULTS	COMMENTS ON SAFETY
Depression accompanying chronic illness and convalescence from short-term illness; mild depression induced by life pressures; over-tranquilization.	"The drug gave a plateau type of stimulation, smooth onset, with no euphoria . . . The effect lasted about four hours, gave the patient a feeling of well-being . . ."	"The side effects of Ritalin are minimal." "The work showed that the drug had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia."[1]
Lethargy, fatigue and emotional depression secondary to chronic illness in elderly patients; mild depression secondary to short-term illness. (Twenty-three "normal," healthy people also received the drug.)	"For the entire 112 patients 66 per cent showed marked improvements [obvious drug effect and mood improvement] . . ."	"No serious side reactions were noted . . . In no case was it necessary to stop the drug. No evidence of significant effect upon blood pressure or pulse has been found. This is particularly interesting, since these side effects have been common with other mood elevating drugs . . ."[2]
Drug-induced psychophysiologic depression; physiologic after-effects of certain anesthetics; barbiturate intoxication; moribund states due to systemic infection. (All patients were epileptic, mentally retarded and/or brain damaged.)	"All except two [of 129] patients responded to the initial injection [of parenteral Ritalin] within 1½ to 15 minutes."	"In no instance was there any evidence of untoward effects." ". . . the very poor basic physical condition of our patients in this study, those associated with profound chronic brain damage, accentuates the safety of parenteral Ritalin . . ."[3]

DOSAGE: *Oral:* Dosage will depend upon indication and individual response. Many patients respond to 10 mg. b.i.d. or t.i.d. Others will require 20-mg. doses. In a few cases, 5-mg. doses will be adequate. If inability to sleep is encountered, last dose should be given before 6 p.m. *Parenteral:* 10 to 30 mg., intravenously or intramuscularly. RITALIN® hydrochloride (methylphenidate hydrochloride CIBA)

REFERENCES: 1. Natenshon, A. L.: Dis. Nerv. System *17*:392 (Dec.) 1956. 2. Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey *55*:55 (Feb.) 1958. 3. Carter, C. H., and Maley, M. C.: Dis. Nerv. System *18*:146 (April) 1957.

2/2593MK

CIBA
SUMMIT, N. J



The highly effective antibacterial, antifungal STEROSAN combined with anti-inflammatory, antipruritic hydrocortisone provides rapid healing in a *wider* range of infective and allergic skin disorders. STEROSAN-Hydrocortisone is superior to either drug used alone and is effective where many antibiotic-hydrocortisone preparations fail.[1] Virtually non-irritating and non-sensitizing, STEROSAN-Hydrocortisone has the added advantage of being odorless, non-greasy, nonstaining, and scarcely perceptible on the skin.

1. Pace, B. F.: M. Rec. & Ann. *51*:370, 1957.

STEROSAN®—Hydrocortisone (3% chlorquinaldol GEIGY with 1% hydrocortisone) Cream and Ointment. Tubes of 5 Gm. and 20 Gm. Prescription only.

GEIGY

ARDSLEY, NEW YORK

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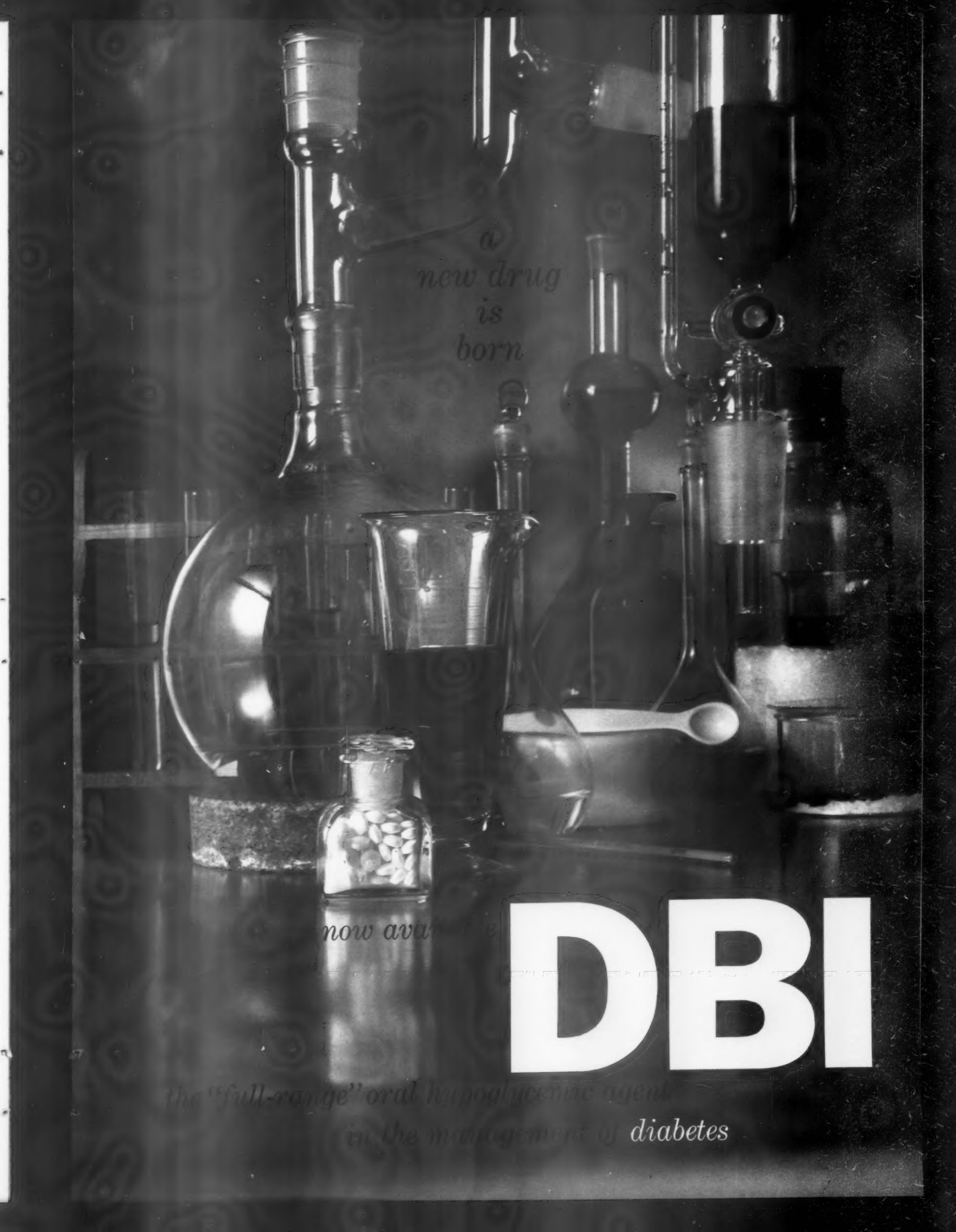

a
new drug
is
born
now ava
DBI
the "full-range" oral hypoglycemic agent
in the management of
diabetes

the "full-range" oral hypoglycemic agent

Trademark

unique compound – DBI (N^1-β-phenethylbiguanide HCl) is an entirely new oral hypoglycemic compound, different in chemical structure and mode of action from the sulfonylureas . . . usually effective in low dosage range (50 to 150 mg. per day).

"full-range" hypoglycemic action – DBI lowers elevated blood sugar and eliminates glycosuria in *mild, moderate* and *severe* diabetes mellitus . . .

brittle diabetes, juvenile or adult – DBI combined with injected insulin improves regulation of the diabetes and helps prevent the wide excursions between hypoglycemic reactions and hyperglycemic ketoacidosis.

stable adult diabetes – satisfactory regulation of diabetes is often achieved with DBI alone without the necessity for insulin injections.

juvenile diabetes – DBI often permits a reduction as great as 50 per cent or more in the daily insulin requirement.

primary and secondary sulfonylurea failures – DBI alone, or in conjunction with a sulfonylurea, often permits satisfactory regulation of diabetes in patients who have failed to respond initially or who have become resistant to oral sulfonylurea therapy.

smooth onset—less likelihood of severe hypoglycemic reaction – DBI has a smooth, gradual blood sugar lowering effect, reaching a maximum in from 5 to 6 hours, and a return to pre-treatment levels usually in 10 to 12 hours.

safety – daily administration of DBI in therapeutic dosage for varying periods up to 2½ years has not produced any form of clinical toxicity.

side reactions – side reactions produced by DBI are chiefly gastrointestinal and occur with increasing frequency at higher dosage levels (exceeding 150 mg. per day). Anorexia, nausea or vomiting may occur – but these symptoms abate promptly upon reduction in dose or withdrawal of DBI.

IMPORTANT – before prescribing DBI the physician should be thoroughly familiar with general directions for its use, indications, dosage, possible side effects, precautions and contraindications, etc.

Write for complete detailed literature.

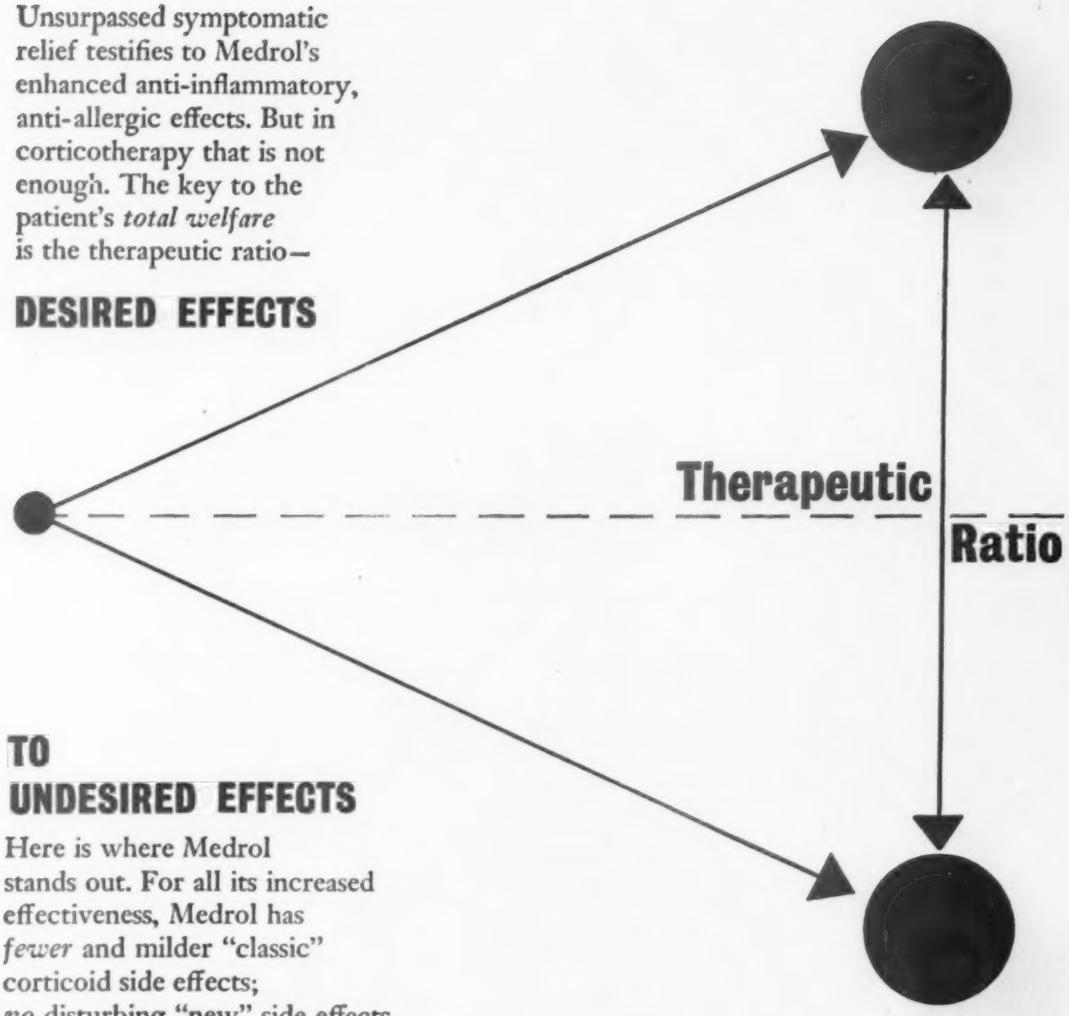
an original development from the research laboratories of

u.s. vitamin & pharmaceutical corporation

Arlington-Funk Laboratories, division
250 East 43rd Street, New York 17, N. Y.

Unsurpassed symptomatic relief testifies to Medrol's enhanced anti-inflammatory, anti-allergic effects. But in corticotherapy that is not enough. The key to the patient's *total welfare* is the therapeutic ratio—

DESIRED EFFECTS



TO
UNDESIRED EFFECTS

Here is where Medrol stands out. For all its increased effectiveness, Medrol has *fewer* and milder "classic" corticoid side effects; *no* disturbing "new" side effects such as muscle weakness. Whenever corticotherapy is indicated, remember that Medrol has the *best therapeutic ratio in the steroid field.*

Medrol hits the disease, but spares the patient

The best therapeutic **ratio in the steroid field makes**

Medrol*

the choice of physicians who consider the total welfare of their patients

*Trademark, Reg. U. S. Pat. Off.—methylprednisolone, Upjohn

Upjohn The Upjohn Company, Kalamazoo, Michigan

To the relief of musculoskeletal pain, new MEDAPRIN* adds restoration of function

Analgesics offer temporary relief of musculoskeletal pain, but they merely *mask* pain rather than getting at its *cause*. New Medaprin, in addition to bringing about prompt subjective improvement, promotes the *restoration of normal function* by suppressing the inflammation that *causes* the pain.

Medaprin, Upjohn's new analgesic-steroid combination, contains aspirin plus Medrol,** the corticosteroid with *the best therapeutic ratio in the steroid field.*† Instead of suffering recurrent discomfort because of the "wearing off" of analgesics, the patient on Medaprin experiences a smooth, *extended* relief and more normal mobility.

Indications: Medaprin is indicated in mild-to-moderate rheumatic and musculoskeletal conditions, including rheumatoid arthritis, deltoid bursitis, low back pain, neuralgia, synovitis, fibromyositis, osteoarthritis, low back sprain, traumatic wrist, sciatica, and "tennis elbow."

Dosage: The recommended dosage is 1 tablet q.i.d. The usual cautions and contraindications of corticotherapy should be observed.

Supplied: In bottles of 100 and 500.

Formula: Each Medaprin tablet contains

- 300 mg. acetylsalicylic acid, for prompt relief of pain
- 1 mg. Medrol, to suppress the causative inflammation
- 200 mg. calcium carbonate, as buffer

*TRADEMARK **TRADEMARK, REG. U. S. PAT. OFF.— METHYLPREDNISOLONE, UPJOHN
†RATIO OF DESIRED EFFECTS TO UNDESIRED EFFECTS

The Upjohn Company, Kalamazoo, Michigan

Upjohn

NEW
anticholinergic / antispasmodic / tranquilizer
A SENTRY FOR THE G.I. TRACT

NEW: A SENTRY FOR THE G.I. TRACT

Since G.I. disorders present multiple difficulties, perhaps you will welcome *one* medication that combats the most prominent and most troublesome symptoms.

ENARAX *protects against*

hypersecretion
hypermotility
hyperirritability
hyperemotivity

ENARAX combines a new long-acting anticholinergic (antisecretory-antispasmodic[1]) with the proven antisecretory-tranquilizer[2-6] (ATARAX®) to relieve pain, spasm, hyperacidity and disease-induced tension. With this unique anticholinergic, just two tablets daily proved clinically effective in 428 out of 490 patients with a wide variety of gastrointestinal disorders.[1,2,7]

Selective postganglionic action on the G.I. tract minimizes side effects. Of 512 patients treated to date, reactions were usually mild, transient and easily reversed. Mouth dryness, blurring of vision, dizziness, urinary hesitancy either disappeared with continued use or were controlled by reducing the dosage.

ENA

ENARAX one tablet at breakfast
one tablet at bedtime

full-time relief in

peptic ulcer	gastritis	duodenitis
functional bowel syndrome	gastroenteritis	hiatus hernia (symptomatic)
ulcerative colitis	pylorospasm	genitourinary spasm
biliary tract dysfunctions	cardiospasm	dysmenorrhea

Each ENARAX tablet contains:
Oxyphencyclimine HCl . . . 10 mg.,
Hydroxyzine HCl (ATARAX®) . . . 25 mg.

Dosage: One-half to one tablet twice daily – preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy or glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: **1.** McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, California, January 27, 1958. **2.** Strub, I. H., and Carballo, A.: To be published. **3.** Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1957. **4.** Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. **5.** La Barre, J.: Compt. rend. Soc. Biol. (Paris) *150*:1807 (Oct.) 1956. **6.** Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957. **7.** Data in Roerig Medical Department files.

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

coming soon

SQUIBB

Squibb Quality - the Priceless Ingredient

NEW
RAUTRAX

RAUDIXIN plus an entirely new diuretic

a natural companion to
famous RAUDIXIN
to help solve the problem–

HYPERTENSION

SQUIBB

RAUDIXIN® AND RAUTRAX ARE SQUIBB TRADEMARKS

in vaginitis

IMPROVED

TRICOFURON®

destroys all 3 *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

℞ NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

B.I.D.

ULCER CONTROL

all day

NEW

DARICON*

oxyphencyclimine hydrochloride

TABLETS

all night

patient comfort

Natural Prolonged Action–The action of DARICON, a more potent and better tolerated anticholinergic, is consistently prolonged because it has a unique chemical structure and is not dependent on "mechanical" means (e.g., special coating, adsorption on ion-exchange resin).

In addition to peptic ulcer, DARICON, is also indicated for other gastrointestinal disorders characterized by hypersecretion, hypermotility and spasm (e.g., functional bowel syndrome. chronic nonspecific ulcerative colitis and biliary tract disease).

Dosage: 10 mg. b.i.d. (morning and evening). **Supply:** Tablets, 10 mg., white, scored. Bottles of 60 and 500.

*Trademark

EVEN REFRACTORY CASES RESPOND

Pfizer Science for the world's well-being

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
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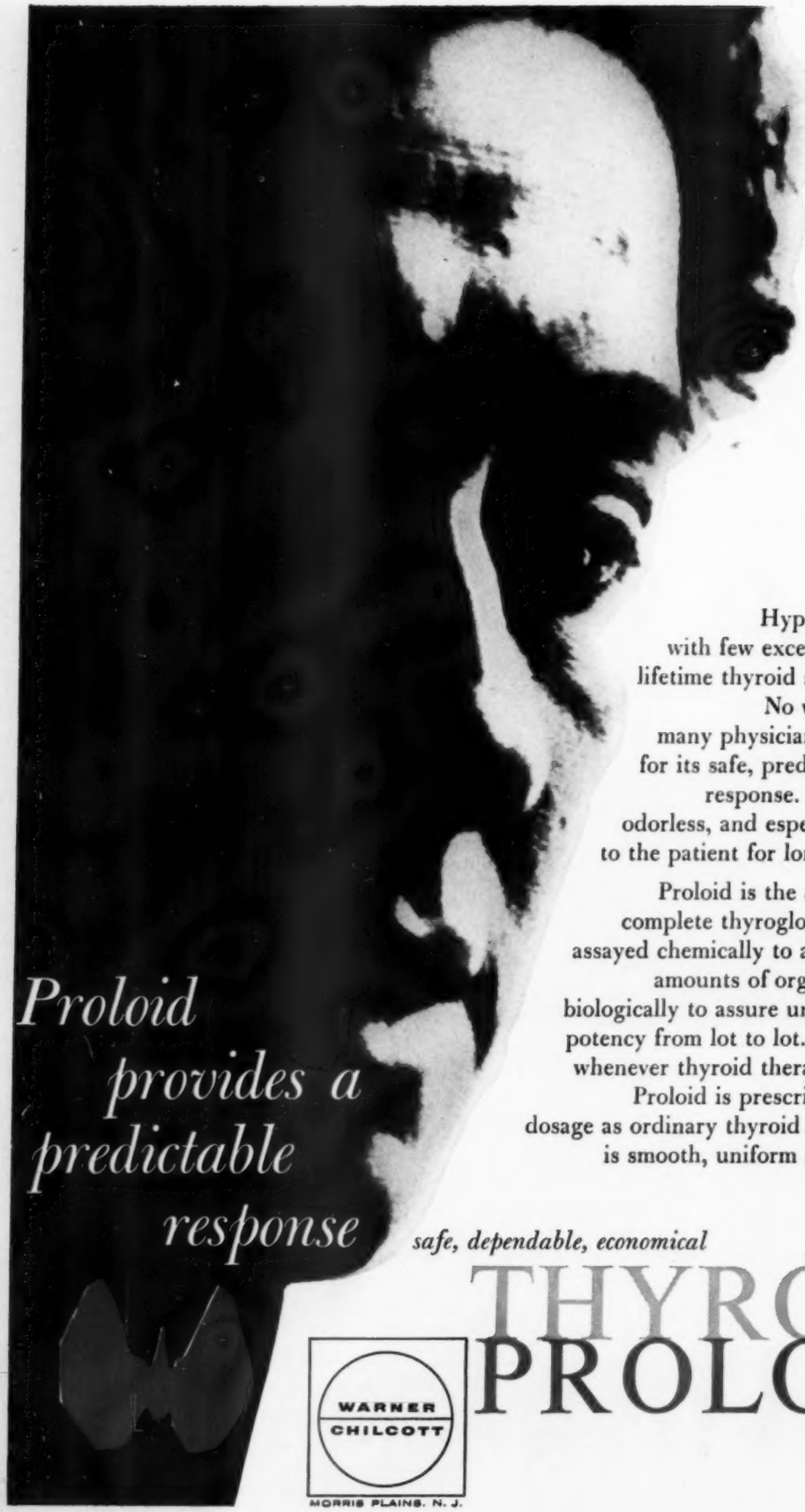

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[1]Halpern, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 28) 1955.

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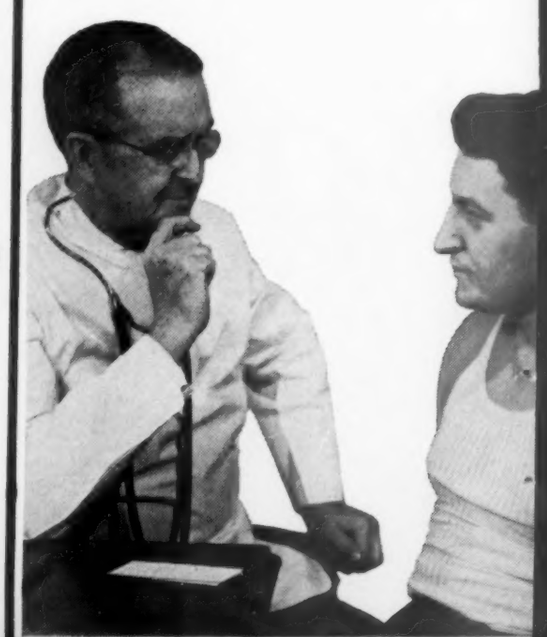
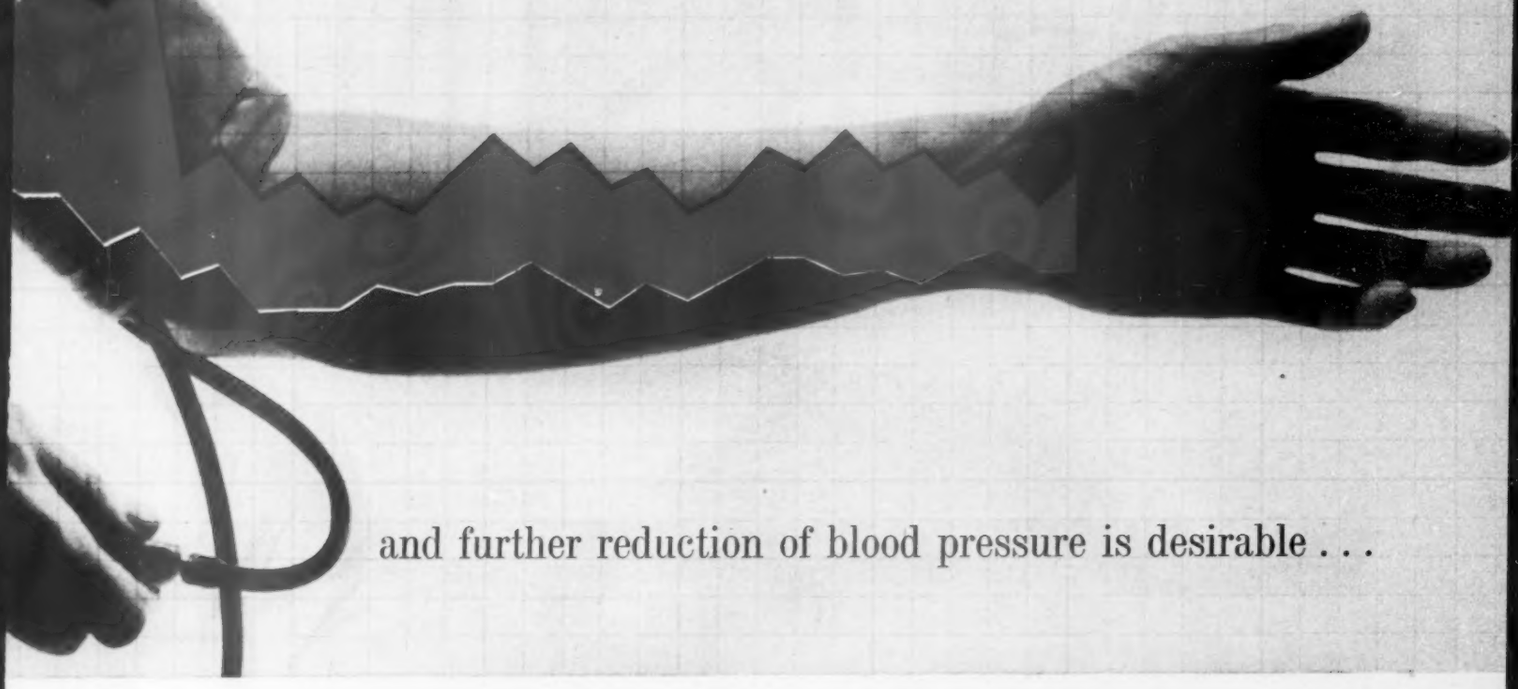


when the response to other hypotensive agents is inadequate . . .



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A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

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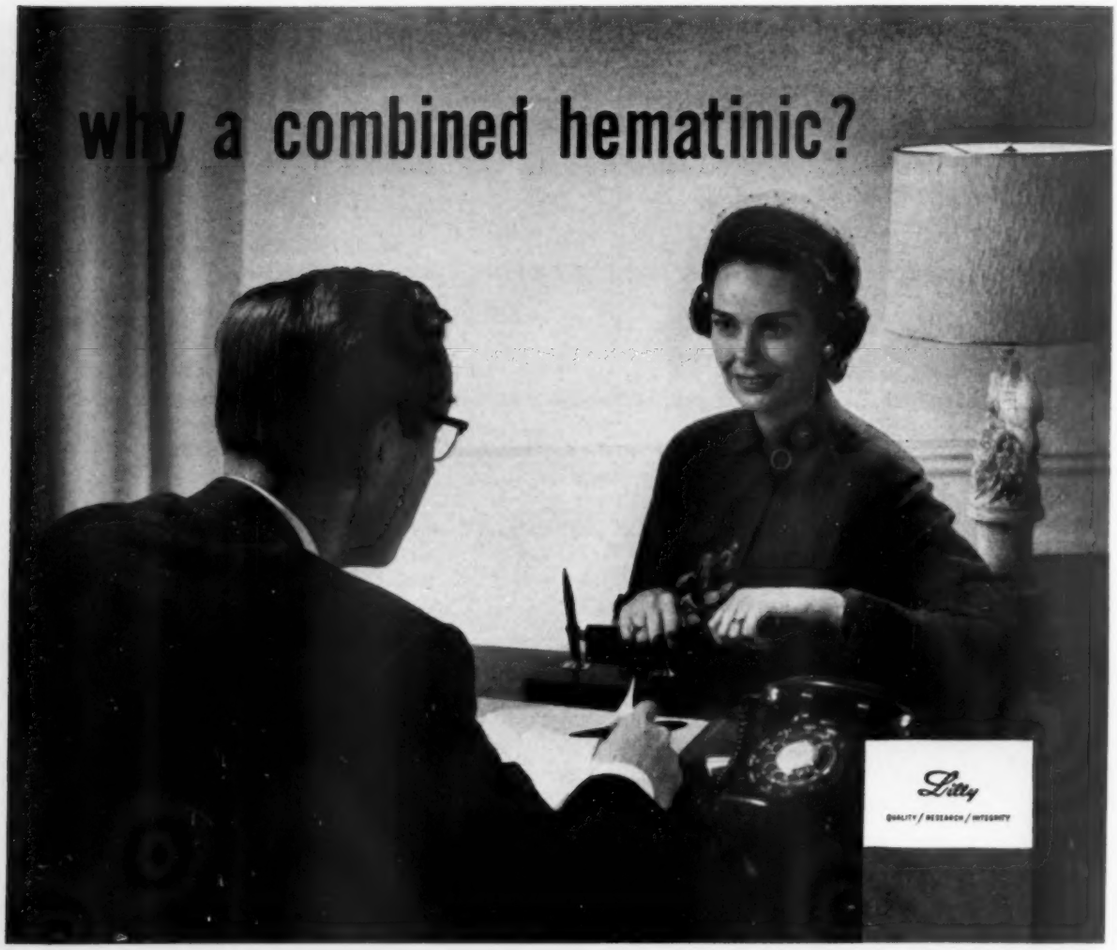

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1. A. M. A. Arch. Int. Med., *99*:346, 1957.
2. Am. J. Obst. & Gynec., *70*:1309, 1955.
3. Lancet, *1*:448, 1957.

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The American Journal of Medicine

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Editorial

Selective Hypoaldosteronism

FROM the time when Conn [*1,2*] proved the existence of selective, primary excess of aldosterone and described its clinical manifestations, it was inevitable that clinicians would be on the watch for the opposite condition, selective deficiency of aldosterone secretion by the adrenal cortex. Two cases have now been recorded in detail which purport to represent instances of this condition, one reported from Boston by Hudson, Chobanian and Relman [*3*] and one by Skanse and Hökfelt of Stockholm [*4*]. Both cases fulfill what must surely constitute the indispensable minimal criteria, in that in both instances there was demonstrated (1) a marked decrease (in the Swedish case, absence) of aldosterone excretion in the urine under circumstances in which it should be present in quantity, and (2) integrity of the glucocorticoid function of the adrenal cortex. Both patients were shown to have a normal carbohydrate metabolism either by the insulin-glucose test of Engel, or by a standard insulin tolerance and glucose tolerance test; to exhibit a normal diuretic response to ingested water; and to respond normally to the intravenous or intramuscular administration of corticotropin, both in terms of the eosinophil response and of the increment in 17-ketosteroids and other steroids reflecting the secretion of adrenocortical steroids.

The clinical features of the two cases, however, were very different. The patient of Skanse and Hökfelt presented herself with complaints of severe recurrent dizziness, weakness, easy fatigability and occasional faints. There was hypotension but no postural hypotension, although the heart rate increased slightly when the patient stood. The serum sodium was found initially to be 136 mEq./L., the normal range in the laboratory being reported as 141 to 150 mEq./L. Renal sodium conservation in response to the administration of a salt-poor diet was entirely normal, but a striking and suggestive feature of this experiment was a sharp rise in the urinary excretion of hydrocortisone and cortisone with salt restriction, a response which does not occur in normal persons [*5*]. There was no evidence of renal disease by the conventional means of clinical study. The excellent renal sodium conservation in the face of drastic dietary sodium deprivation, as well as the sharp fall in urinary sodium excretion which could be produced by injection of ACTH, indicated that there was no intrinsic inadequacy or unresponsiveness of the renal tubular sodium-conserving mechanism.

Since sodium conservation in the urine appeared to be entirely adequate in the face of

[1] CONN, J. W. Presidential Address. II. Primary aldosteronism, a new clinical syndrome. *J. Lab. & Clin. Med.*, 45: 6, 1955.

[2] CONN, J. W. and LOUIS, L. H. Primary aldosteronism: new clinical entity. *Tr. A. Am. Physicians*, 68: 215, 1955.

[3] HUDSON, J. B., CHOBANIAN, A. V. and RELMAN, A. S. Hypoaldosteronism. A clinical study of a patient with an isolated adrenal mineralocorticoid deficiency, resulting in hyperkaliemia and Stokes-Adams attacks. *New England J. Med.*, 257: 529, 1957.

[4] SKANSE, B and HÖKFELT, B. Hypoaldosteronism with otherwise intact adrenocortical function, resulting in a characteristic clinical entity. *Acta endocrinol.*, 28: 29, 1958.

[5] CRABBÉ, J., REDDY, W. J., ROSS, E. J. and THORN, G. W. Role of adrenal cortex in normal adaptation to dietary sodium deprivation. *J. Clin. Endocrinol. & Metab.*, 18: 1147, 1958.

drastic dietary salt deprivation, it is not immediately evident that the hyponatremia could be attributed to hypoaldosteronism, which would presumably only affect serum sodium concentration (in the presence of excellent glucocorticoid function) by permitting salt waste in the urine. It might be argued that the conservation of sodium was inefficient insofar as it became adequate only after the serum sodium concentration had fallen; but there seems to be a question about the hyponatremia itself, since in the graphic presentation of the results of feeding the low-sodium diet the serum sodium concentration appears to have been maintained close to 140 mEq./L. throughout. Moreover, if any or all the symptoms were due to a selective deficit of aldosterone one would expect that they would be completely relieved by the administration of desoxycorticosterone. In the event, one month after an injection of 50 mg. of desoxycorticosterone as microcrystals, the patient reported that the dizzy spells continued unabated, although faints had not occurred. It is noteworthy also that the injection of 3 mg. of desoxycorticosterone acetate (DCA) intramuscularly daily did not increase the serum sodium concentration, although indeed the initial concentration measured before this therapy (140 mEq./L.) was scarcely abnormal.

In the Boston case the clinical features which were thought to be indicative of selective aldosterone deficit were (1) hyperkalemia, (2) inefficient renal sodium conservation when a salt-poor diet was fed, and (3) improvement of sodium conservation, together with increased potassium clearance, when under these circumstances desoxycorticosterone was administered. The evidence presented with regard to the second and third points consisted of observations of the patient over a two-week period during consumption of a diet providing 8 mEq. of sodium daily, followed by a week of the same regimen plus the administration of 5 to 15 mg. of DCA daily. During the first week the excretion of sodium in the urine fell from about 30 to approximately 20 mEq. daily, during the second week little change occurred, and during DCA administration urinary sodium excretion almost ceased. The serum sodium concentration fell from about 140 to 133 mEq./L. during the first two weeks. In a third metabolic period it was demonstrated that the administration of DCA promoted renal sodium retention and potassium excretion when salt was provided liberally in the diet.

Shortly before, this patient had been under treatment for severe congestive circulatory failure but had been clinically compensated without dietary salt restriction for several weeks prior to the study. A normal person without occult edema would indeed come into approximate sodium balance on the fifth day of the metabolic regimen employed, but an appropriate although subnormal renal sodium-conserving response over a two-week period by a patient of this sort is difficult to interpret. Absence of visible edema does not exclude residual expansion of extracellular fluid volume by several liters at least, corresponding to some 300 mEq. of sodium, much of which would presumably tend gradually to be mobilized and appear in the urine upon drastic salt restriction.

The authors also imply that good renal conservation of sodium in response to injection of DCA establishes wholly normal intrinsic responsiveness of the renal tubular sodium-conserving mechanism to stimuli (such as aldosterone secretion) which would ordinarily be called forth by dietary salt restriction; but this view is not warranted by any evidence cited. It is true that one may observe marked failure of tubular sodium conservation in severe renal disease with fixed azotemia which is not responsive to the administration of DCA [*6*]; but there must evidently exist earlier stages of the tubular abnormality of which that condition is the end stage, and in such an earlier stage one would surely expect that under the influence of large quantities of DCA the tubules might conserve sodium and chloride more effectively than they do in response to moderate sodium depletion. The evidence that the apparent impairment of sodium conservation in this patient was due to insufficient aldosterone secretion seems not wholly convincing.

With regard to the hyperkalemia, it is notable that none was present initially, that the first definite elevation of serum potassium (6.8 mEq./L.) was found immediately after a convulsion due to a Stokes-Adams attack, that heart block with bradycardia invariably accompanied even moderate hyperkalemia, and that all the subsequent marked elevations of serum potassium were found soon after further convulsive episodes. One wonders whether reduced cardiac output and renal blood flow, intermittent

[6] Thorn, G. W., Koepf, G. F. and Clinton, M., Jr. Renal failure simulating adrenocortical insufficiency. *New England J. Med.*, 231: 76, 1944.

anoxia, and some degree of renal disease could not together account for the hyperkalemia. Hudson et al. were of the opinion that hyperkalemia precipitated cardiac conduction difficulties because in one experiment cardiac standstill, preceded by ventricular slowing, occurred when the serum potassium was raised by infusing potassium chloride. But even if the point be granted, the reverse relationship is thereby not ruled out; and no satisfactory explanation is furnished of the decrease by 1.6 mEq./L. of serum potassium concentration to normal which occurred over a period of twenty-four hours or less following the first syncopal attack, or of the similar and considerably larger decrease to normal observed within twenty-four hours after the last two reported cardiac standstills.

Some of the physiologic and clinical data offered in support of the diagnosis of selective hypoaldosteronism in each of these cases, individually considered, are thus open to some question. Comparison of the two cases brings out the remarkable fact that, except for very slight hyponatremia, the two cases had no common clinical features whatever, the findings being actually antithetical: faints and dizzy spells, excellent renal salt conservation and normal potassium metabolism, contrasted with congestive failure, hyperkalemia and defective renal salt conservation correctable by the administration of DCA. Can two such disparate syndromes possibly both reflect the same condition? If not, which syndrome seems more likely to result from selective hypoaldosteronism?

Information relevant to this question must, one would think, be available, since rather extensive experience has now accumulated [*7–12*] with patients whose condition should very closely simulate primary selective aldosterone deficit, namely adrenal-deficient persons—especially those who have had total bilateral adrenalectomy performed—who are being maintained on steroid replacement therapy *not* including any potent mineralocorticoid compound such as DCA, aldosterone or 9-alpha-fluorohydrocortisone, but with liberal dietary sodium chloride intake. Many such patients, taking cortisone acetate only in a divided daily dose of 50 mg., have been observed to remain asymptomatic for weeks or months, and to maintain apparent electrolyte balance and satisfactory if not wholly normal concentrations of serum electrolytes. Such manifestations of adrenal inadequacy as they develop from time to time under stress are, generally speaking, those of classic acute or subacute adrenal insufficiency, of which the milder manifestations are fatigue, weakness, anorexia, and especially the symptoms and signs of postural hypotension. Most notably, hyperkalemia seldom occurs unless accompanied by the aforementioned symptoms, and generally with falling serum sodium concentration. It has also been observed [*13*] that patients with Addison's disease of spontaneous origin may continue to show hypotension while receiving cortisone in amounts sufficient to restore entirely their appetite and well-being, and to prevent postural hypotension.

On the basis of this experience one would judge that the findings in the patient of Skanse and Hökfelt approximated more closely what one would expect in advance to find in a patient with primary selective aldosterone deficiency than did those in the patient of Hudson et al. Nevertheless, certain observations recorded by the writer and his colleagues suggest the likelihood that a syndrome more like that of the patient of Hudson et al. might also be the clinical expression of primary selective hypoaldosteronism, provided that intrinsic renal disease is coincidentally present.

Hills, Zintel and Parsons [*11*], in a four-year study of seventeen totally and twenty-seven subtotally adrenalectomized patients maintained for considerable periods of time on cortisone as the sole replacement therapy, observed that in two of these patients, both subtotally adrenalec-

[7] Thorn, G. W., Harrison, J. H., Merrill, J. P., Criscitiello, M. G., Frawley, T. F. and Finkenstaedt, J. T. Clinical studies on bilateral complete adrenalectomy in patients with severe hypertensive vasular disease. *Ann. Int. Med.*, 37: 972, 1952.

[8] Pearson, O. H., Whitmore, W. F., Jr., West, C. D., Farrow, J. H. and Randall, H. T. Clinical and metabolic studies of bilateral adrenalectomy for advanced cancer in man. *Surgery*, 34: 543, 1953.

[9] Garrod, O., Nabarro, J. D. N., Pawan, G. L. S. and Walker, G. Metabolic effects of 9α-fluorohydrocortisone and of cortisone in adrenal insufficiency. *Lancet*, 2: 367, 1955.

[10] Bergenstal, D. M., Huggins, C. and Dao, T. L.-Y. Metabolic effects of adrenalectomy in man. The human adrenal cortex. In: Ciba Foundation Colloquia on Endocrinology, vol. 8, p. 415. Boston, 1955. Little, Brown & Co.

[11] Hills, A. G., Zintel, H. A. and Parsons, D. W. Observations of human adrenal cortical deficiency, with special reference to replacement therapy with cortisone. *Am. J. Med.*, 21: 358, 1956.

[12] Hart, D. F. Treatment of adrenocortical deficiency states. *Brit. M. J.*, 1: 417, 1957.

[13] Hills, A. G. Unpublished data.

tomized persons, treatment with moderate doses of cortisone alone proved unsatisfactory, and a potent mineralocorticoid compound was required. This was not because of the appearance of the symptom complex described, but because hyperkalemia and azotemia, without other disorders, appeared when cortisone alone, in a dose up to 50 mg. daily, was provided. There appeared to be a similar tendency in several of the other patients, although it was not as easily documented. All these patients gave evidence of impairment of renal function. The resemblance of the syndrome exhibited by these patients to that of the patient of Hudson et al. is evident, and these authors in fact cited it, together with unpublished observations of Relman, as an indication that patients with selective hypoaldosteronism will have "a continuous tendency to high potassium levels that is most apparent when the sodium intake is low." But as already noted, hyperkalemia without the collateral evidences of adrenal insufficiency is uncommon in totally adrenalectomized patients on maintenance cortisone therapy; and in the two patients reported by us in whom azotemia and hyperkalemia frequently were observed as isolated evidences of hypoadrenalism, these findings could not be ascribed to a low dietary salt intake by the patients. Both of them used salt freely in their cooking and at the table during the period reported. From this one must conclude that their self-selected intake of sodium was comparable to that of the other patients, who were shown, on the basis of single or multiple determinations of twenty-four hour urine sodium excretion by a 20 per cent random sample of the patient material, to select diets of average sodium content, corresponding to an intake of 4 to 12 gm. of sodium chloride daily. In addition both the patients in question were on occasion given enteric-coated salt supplements, 3 gm. daily and 6 gm. daily, respectively, and it was observed that this therapy failed to control the hyperkalemia and azotemia satisfactorily. The tendency to azotemia and hyperkalemia was in fact a constant characteristic of these two patients throughout the period of observation. In one of them (S. W.) it was displayed in two separate metabolic balance studies of the effect of hormone withdrawal while the patient was on a constant dietary regimen [*11*], and these studies, in which 285 mEq. of sodium daily was provided during the control period, may be compared [*14*] with similar studies in other adrenal-deficient patients who generally received less dietary sodium during the experiment, yet in whom hyperkalemia and azotemia did not develop out of proportion to the other manifestations of adrenal insufficiency.

Explanation of the findings was based on the facts (1) that the special tendency of such patients to selective hyperkalemia and azotemia represented a modification in them of the usual physiologic expression of adrenal insufficiency by some concurrent abnormality characteristic of the individual organism, and (2) that neither glucocorticoids in moderate dosage nor a liberal salt intake adequately controlled the condition which, however, responded quite specifically to provision of a mineralocorticoid compound. It was therefore suggested [*11,14*] that the peculiar response of the two patients in question to adrenal deficiency was ascribable to renal damage probably resulting from their previous hypertensive disease and involving, whether selectively or simply as an aspect of pannephropathy, the renal mechanism for the secretion or reabsorption of potassium.

At the time these observations were reported it seemed somewhat surprising, on the basis of the explanation offered, that there should occur a rather striking parallelism of azotemia and hyperkalemia under these circumstances; for the principal nitrogenous constituent of the plasma, urea, was known to be filtered at the glomerulus, and the reabsorption which was known to occur was thought to be a wholly passive process of diffusion [*15*]. It is now known [*16*] that an active mechanism (or mechanisms) exists for transporting urea across the renal tubule, and evidence has been secured [*17*] that tubular reabsorption of urea, compared at any corresponding rate of urine flow with normal subjects, is characteristically excessive in adrenal insufficiency in man. These developments permit ascription of the azotemia as well as the hyperkalemia, in

[14] Hills, A. G., Webster, G. D., Jr., Rosenthal, O., Dohan, F. C., Richardson, E. M., Zintel, H. A. and Jeffers, W. A. Quantitative evaluation of primary adrenal cortical deficiency in man. *Am. J. Med.*, 16: 328, 1954.

[15] Smith, H. W. The Kidney. Structure and Function in Health and Disease. New York, 1951. Oxford University Press.

[16] Schmidt-Nielsen, B. Urea excretion in mammals. *Physiol. Rev.*, 38: 139, 1958.

[17] Hills, A. G., Parsons, D. W., Rosenthal, O. and Kiem, I. Excessive renal tubular reabsorption of filtered urea in human adrenal insufficiency. *J. Clin. Invest.* (In press.)

part if not principally, to disordered function of the renal tubular epithelial cells in adrenal insufficiency, although whether the two tubular disorders are as closely related physiologically as they have been clinically in these patients is open to question.

Granting that caution is indicated in attributing the several manifestations observed in the Boston and Stockholm cases to selective hypoaldosteronism, the fact remains that in each case it was convincingly demonstrated that urinary aldosterone excretion was absent or notably subnormal. It is known that diminished urinary excretion of other types of steroids used to assess adrenal cortical function, notably 17-ketosteroids [*18*], does not necessarily indicate adrenal deficiency; perhaps it is too early to be sure that non-specific depression of urinary aldosterone excretion may not also occur. It seems warranted, nevertheless, to accept the Stockholm case as a probable instance of uncomplicated selective hypoaldosteronism, and to regard the Boston case, whatever its pathophysiology, as presenting features suggestive of a different syndrome which may be anticipated should selective hypoaldosteronism supervene in patients with intrinsic renal disease. A definite conclusion might well be postponed, however, until additional clinical, physiologic and pathologic information concerning the condition in question has been accumulated.

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[18] Dorfman, R. I. and Shipley, R. A. Androgens. Biochemistry and Clinical Significance, chap. 20. New York, 1956. John Wiley & Sons.

Clinical Studies

The Identification and Quantification of Left-to-Right Circulatory Shunts*

A New Diagnostic Method Utilizing the Inhalation of a Radioactive Gas, Kr^{85}

RICHARD J. SANDERS, M.D. *and* ANDREW G. MORROW, M.D.
Bethesda, Maryland

A LARGE proportion of patients with congenital cardiovascular anomalies resulting in left-to-right circulatory shunts may now be offered completely corrective operations. In the selection of such patients for operation and in the physiological assessment of the operative result, the need for more precise methods of localization and quantification of left-to-right shunts has become apparent. The characterization of such shunts by determinations of the oxygen content of blood from the great vessels and cardiac chambers may be difficult because of several inherent limitations of this method. Principally, these are concerned with changes in the metabolic state which may occur during the sampling period and the difficulty in obtaining representative samples of mixed venous blood from the venae cavae.

Recently it has been demonstrated that the large arteriovenous difference which exists shortly after the inhalation of an inert gas may be utilized to provide an improved method for the detection of a left-to-right shunt and also to funrnish an estimate of its magnitude. Nitrous oxide was first used for this purpose, and this technic was found both simpler and more accurate than oximetry in large clinical series [*1,2*]. The superiority of the N_2O test was attributable to the independence of N_2O levels from metabolic changes, and the elimination of vena caval sampling. Since the analysis of blood samples for N_2O content was found both difficult and time consuming, other inert gases that might be equally useful, yet easier and faster to assay, were sought. Various radioactive gases were therefore considered and after experimental evaluation of two, trifluoroiodomethane (CF_3I^{131}) and krypton^{85} [*3*], the latter was selected for clinical trial [*4*].

The present report describes the technic and applications of the Kr^{85} test and compares its accuracy to that of the N_2O test and the standard method of measuring oxygen differences.

MATERIAL AND METHOD

A total of 125 Kr^{85} tests were performed in eighty-three patients. Fifty-six "control" tests were performed in forty-five patients, twenty-five with rheumatic heart disease and twenty with congenital heart disease, but without left-to-right shunts. Sixty-nine tests were performed at or distal to the termination of a shunt in thirty-eight patients; eighteen had shunts into the right atrium, fifteen into the right ventricle, and five into the pulmonary artery.

The presence or absence of a shunt was established in all patients at operation, autopsy, or by the application of other diagnostic technics including the N_2O test, indicator dilution curves with left heart injection [*5,6*], selective angiography or aortography [*7,8*] and left heart and aortic catheterization [*9,10*].

Kr^{85} was administered in the course of right heart catheterization. The tip of a cardiac catheter was positioned in the pulmonary artery or in the outflow tract of the right atrium or right ventricle, and an indwelling needle was inserted into a systemic artery. The patient was then instructed to hyperventilate a mixture of approximately 4 mc./L. of Kr^{85} in air, either from a spirometer or a small compression

* From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

cylinder.* In some instances the Kr^{85} was mixed with 50 per cent N_2O instead of air so that both Kr^{85} and N_2O tests could be performed simultaneously. The gas was administered through a mask or mouth piece connected to a Collins three-way valve. When the spirometer was used, the patient exhaled into the spirometer during the test, and into a collection bag for five minutes after the test. When the compression cylinder was used the flow was regulated either by a demand valve, or a breathing bag and all expired air was directed into a collection bag, both during the test and for five minutes after its completion. The contents of the collection bag were later discarded in a hood. The tests were performed in a well ventilated laboratory, with a Geiger-Müller tube and count-rate meter monitoring the atmosphere continually. Lead shielding around the tank or spirometer was found unnecessary.

The patients inhaled the mixture for thirty seconds, and in a few instances for sixty seconds. Blood samples were drawn simultaneously from the needle and the catheter at various timed intervals during inhalation. Oiled, heparinized Luer-Lok syringes were employed. Samples drawn over five-second periods contained only 2 cc. of blood while integrated samples between the tenth and thirtieth seconds of inhalation usually contained 5 cc. The Kr^{85} content of the blood samples was determined in one of two ways. In the majority of tests, the Kr^{85} was extracted from the blood by adding 2 cc. of air to the syringe and shaking the syringe for one minute while a vacuum was applied to the barrel of the syringe. The air, which then contained the Kr^{85}, was injected into a small chamber fixed over the window of a Geiger-Müller tube. Later in the study, the end window Geiger-Müller tube was replaced by a continuous gas flow tube,† capable of counting beta emissions from Kr^{85} in whole blood. (Fig. 1.) When this tube was employed, the blood was transferred directly from the sampling syringe into the chamber of the counter. When the volume of the sample was not sufficient to fill the chamber, it was diluted: equal amounts of water were added to equal amounts of blood in each pair of syringes, so that the final results of the test were not altered by the dilution. The samples were counted for one minute on a scaler and then washed from the tube by running water followed by compressed air or suction. When the gas was counted with the end-window Geiger-Müller tube, suction alone was used to clean the counting chamber.

FIG. 1. Insertion of a whole blood sample into the continuous gas flow tube for Kr^{85} analysis. The tube is cleaned by running water through the upper stop-cock and out the lower one; this is followed by suction to remove any excess radioactive gas.

Repeat tests were frequently performed in the same or another heart chamber after allowing a period of at least five minutes for Kr^{85} desaturation. A blank specimen was obtained from the catheter immediately prior to each test. The results of each test were expressed as the ratio of the venous sample to the arterial sample:

$$\frac{\text{PA, RV, or RA Count} - \text{Blank Count}}{\text{Arterial Count} - \text{Blank Count}} \times 100 = \text{per cent}$$

PA = pulmonary arterial, RV = right ventricular, RA = right atrial. Background counts usually varied from twenty to thirty counts per minute.

The N_2O tests were carried out similarly except that a gas mixture containing 50 per cent N_2O was inhaled for thirty seconds, while simultaneous integrated arterial and venous blood samples were drawn during the last twenty seconds of inhalation [*2*]. When Kr^{85} was administered simultaneously with N_2O, one half of each blood sample was analyzed for Kr^{85} content and and the other for N_2O. In fifty-four patients, two or three blood samples for O_2 determination were obtained in rapid succession from each right heart chamber and pulmonary artery, and two from each vena cava. Only the average of the O_2 samples from each chamber is presented. The average caval O_2 content was derived by weighting the inferior caval as twice the superior caval value except in those instances in which the inferior cava could not be entered. All of the N_2O and most of the O_2 samples were analyzed

* Kr^{85} was obtained from the Union Carbide Co., Oak Ridge, Tennessee in a mixture of stable gases, containing 1 curie of Kr^{85}. This was mixed with air in a liter flask, so each cc. of air contained 1 mc. Two to four cc. of this mixture were removed, when needed, to recharge the the spirometer. Size D compression cylinders, were prepared by first evacuating them and using the resulting vacuum to draw 80 mc. of Kr^{85} into the cylinder. This was diluted to a concentration of 0.4 mc./L. by adding 200 L. of either air or N_2O under pressure.

† Obtained from Nuclear Corporation of America, Brooklyn, New York.

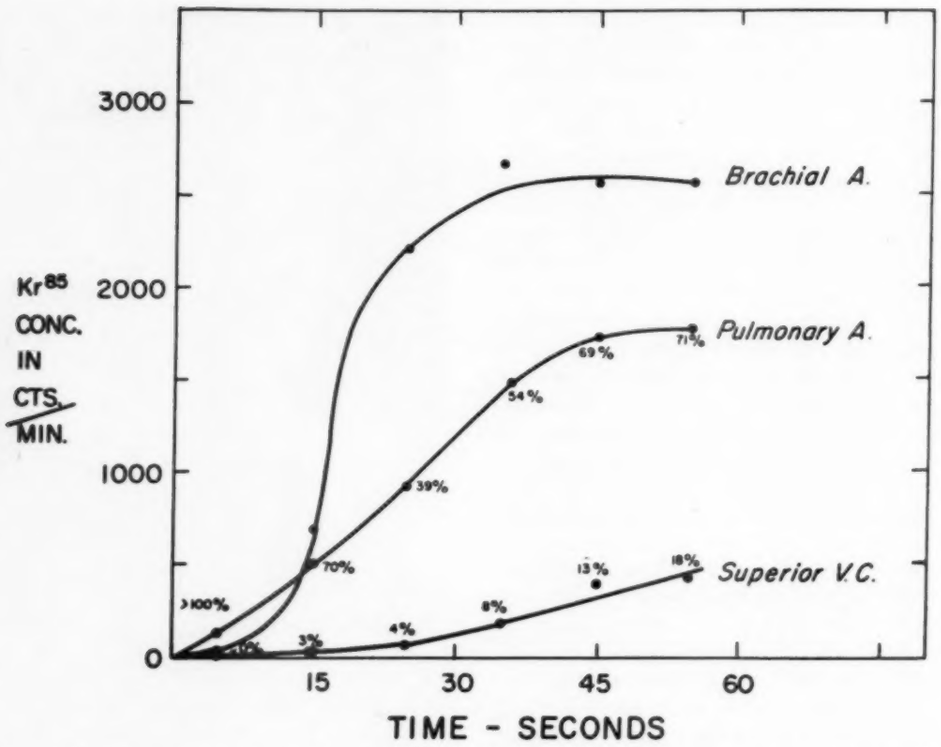

FIG. 2. The changing concentrations of radioactive gas in a systemic artery, and proximal and distal to an atrial septal defect during sixty seconds of Kr^{85} inhalation. The percentages relate the venous samples (SVC and PA) to the corresponding arterial samples. The content of normal venous blood increases gradually, while the content distal to the shunt rises immediately, even before radioactivity is apparent in systemic arterial blood.

manometrically [*11,12*]. In a few patients, O_2 saturation was determined spectrophotometrically [*13*].

RESULTS

The test is based upon the large arteriovenous difference in Kr^{85} content which exists during the early period of inhalation. This is illustrated by the curves obtained from sites proximal and distal to an atrial septal defect. (Fig. 2.) Shortly after the onset of Kr^{85} inhalation, the arterial content rises rapidly and approaches full saturation within one minute. In the absence of, or proximal to a left-to-right shunt, the Kr^{85} content of venous blood remains at zero for at least the first ten or fifteen seconds, and then rises slowly. At the end of the first minute, the radioactivity of mixed venous blood in twelve control patients ranged from 12 to 42 per cent of the arterial content; the lower values were obtained in patients with slow circulation times and the higher values in patients with rapid circulation times. In patients with left-to-right shunts, the radioactivity of blood sampled at or distal to the defect was found to be intermediate between arterial and mixed venous levels (as in the pulmonary arterial curve in Figure 2). An exception to this was noted during the first few seconds of inhalation, when the circulation time between the left side of the heart and the peripheral artery caused a brief delay in the rise of the arterial level.

It is apparent from the curves reproduced in Figure 2, that in the practical application of this principle a single pair of simultaneous samples, relating the radioactivity of right heart to arterial blood, is sufficient to establish the presence or absence of a shunt. The time during which these samples are drawn, however, is of great importance and several different sampling periods were evaluated.

In fifty-five tests, the samples were drawn between the tenth and fifteenth, fifteenth and twentieth, or twentieth and twenty-fifth seconds of inhalation. The results of these tests employing early sampling are summarized in Figure 3. The arterial contents ranged from 200 to 4,000 counts/minute, a range 10 to 200 times the background count. In the twenty-six control tests the

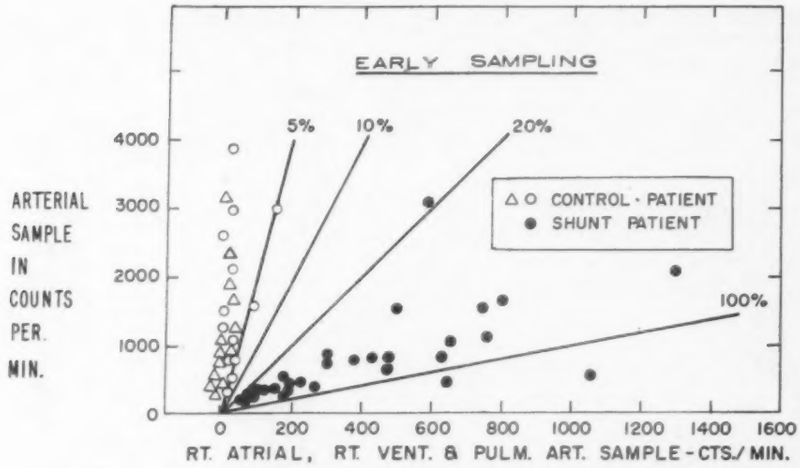

FIG. 3. Comparison of right heart and arterial Kr^{85} samples in patients with and without left-to-right shunts. Early sampling was employed (see text). The control patients are further divided into those with rheumatic (△), and those with congenital (○) heart disease. Percentage lines refer to RA/A, RV/A, or PA/A ratios. A wide zone between 6 and 19 per cent separates the two groups of patients.

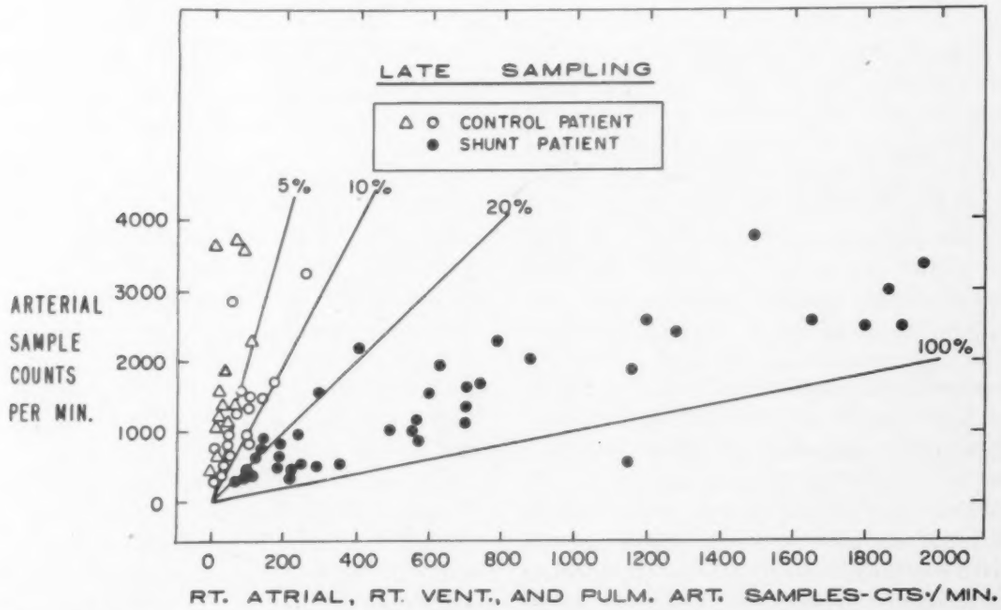

FIG. 4. Right heart and arterial Kr^{85} samples obtained with later sampling (see text). Designation of shunt and control patients as in Figure 3.

radioactivity of pulmonary arterial, right ventricular, or right atrial samples never exceeded 6 per cent of the corresponding arterial levels. In contrast, however, in twenty-eight of the twenty-nine patients with proved left-to-right shunts the radioactivity of samples drawn at or distal to the shunt was 20 per cent or more of the arterial level; in the twenty-ninth patient, the ratio was 19 per cent. Thus, with early sampling, the control patients were easily distinguished from those with a left to right shunt, and the zone of separation was wide.

In seventy tests the samples were drawn either between the tenth and thirtieth, twenty-fifth and thirtieth, or thirtieth and thirty-fifth seconds of inhalation. The results of these tests employing later sampling are summarized in Figure 4. In twenty-seven of the thirty control tests the pul-

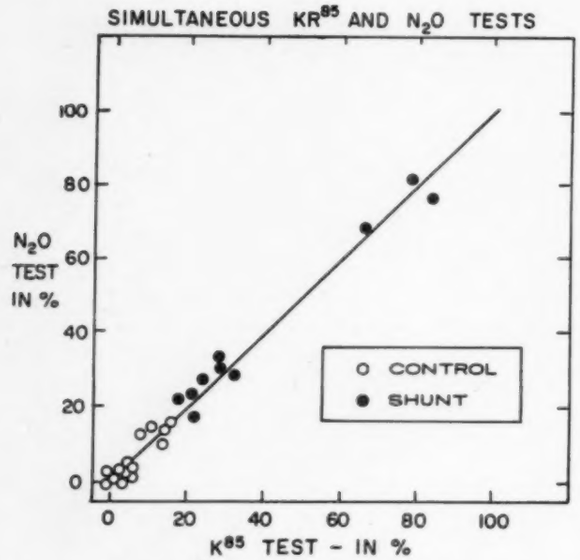

FIG. 5. Comparison of results of twenty-four pairs of simultaneous Kr^{85} and N_2O tests. The Kr^{85} content was determined in all instances by counting whole blood.

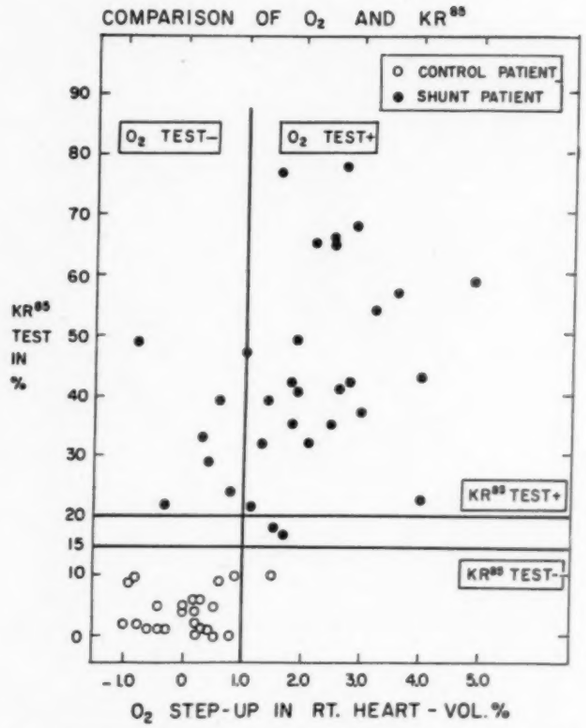

FIG. 6. Comparison of Kr^{85} test with method of O_2 differences in patients with and without shunts.

monary arterial, right ventricular, or right atrial ratio was less than 10 per cent; the remaining three patients had ratios between 10 and 12 per cent. Thirty-five of the forty tests performed beyond left-to-right shunts gave pulmonary arterial or right heart ratios greater than 20 per cent; the other five patients with shunts had ratios between 15 and 20 per cent. Thus, in seventy tests with later sampling, eight ratios between 10 and 20 per cent were observed, and no wide zone of separation between the shunt and non-shunt groups existed, although a line could be drawn between them at 15 per cent. The somewhat different results obtained with early and later sampling were due principally to higher ratios in the non-rheumatic control patients who have, in general, rapid circulation times. All of the patients with rheumatic heart disease had ratios less than 6 per cent with either late or early sampling. Thirteen of the seventeen non-rheumatic control patients had ratios between 6 and 12 per cent with the later sampling periods, whereas they all had levels less than 6 per cent with the earlier sampling period.

Comparison of Kr^{85} and N_2O Tests. In all patients in whom Kr^{85} tests were performed, N_2O tests were also performed at the same sites. Although sampling times in the two tests were not always identical, in the majority of patients the two ratios were within 10 per cent of each other and in no instance, when the criteria of the N_2O test were applied to both, were the results of the two tests in conflict as to the presence or absence of a shunt. At the suggestion of Dr. Robert W. Berliner, sixty tests were carried out in which Kr^{85} and 50 per cent N_2O were administered simultaneously. In this comparative study, the gas extraction technic was used in thirty-six tests and whole blood was counted in twenty-four. Although good correlation with the N_2O test was seen with both methods of Kr^{85} analysis, the results were less at variance when the whole blood-counting technic was employed. (Fig. 5.) Under these circumstances, the results of twenty-three of the twenty-four simultaneous N_2O and Kr^{85} tests differed by no more than 5 per cent.

Comparison of Kr^{85} Test with O_2 Differences. A comparison of the Kr^{85} test with the method of measuring O_2 differences is presented in Figure 6. An increase in blood O_2 content of at least 1.0 volume per cent in the right ventricle or pulmonary artery was considered necessary to establish the presence of a shunt at these sites. An O_2 increase of 1.5 volume per cent in the right atrium is usually considered diagnostic. However, in none of the patients with right atrial shunts studied were increases between 1.0 and 1.5 volume per cent found. Thus the same

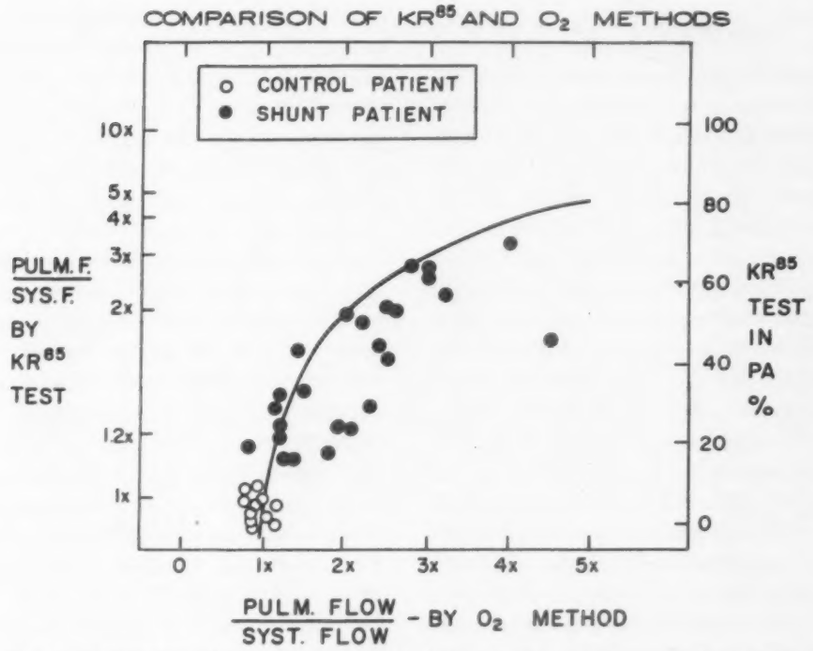

FIG. 7. Estimation of the magnitude of left-to-right shunts, a comparison of the O_2 and Kr^{85} methods. The pulmonary flow: systemic flow ratios by both technics were derived by relating the systemic to the pulmonary arteriovenous difference in O_2 or Kr^{85} content.

diagnostic line of 1.0 volume per cent could be applied to all the patients. Among the thirty-two patients with proved left-to-right shunts, there were six with O_2 differences less than 1.0 volume per cent; in the control group of twenty-two patients, there was one with an O_2 increase greater than 1.0 volume per cent. Thus, the O_2 method was in error as to the correct diagnosis in seven of these fifty-four patients. In comparison, the Kr^{85} tests in these same patients gave ratios of less than 15 per cent in all control patients; in patients with left-to-right shunts the ratios exceeded 20 per cent in all but two instances in which the results were 17 and 18 per cent.

Quantification of the Shunt. The magnitude of a left-to-right shunt could be estimated from the Kr^{85} test, by relating the arteriovenous differences in Kr^{85} content in the systemic and pulmonary circuits. The same mixing formula derived for the N_2O test [2] was applied:

$$\frac{\text{Pulmonary Flow}}{\text{Systemic Flow}} = \frac{Ca - Cvc}{Ca - Cpa}$$

in which Ca, Cvc, and Cpa represent the Kr^{85} concentrations in arterial vena caval, and pulmonary arterial blood respectively. Since the Kr^{85} concentrations are all expressed as percentages of the arterial concentration (100 per cent), and since the concentration of mixed venous blood is approximately 6 per cent (Fig. 4), the formula may be written:

$$\frac{\text{Pulmonary Flow}}{\text{Systemic Flow}} = \frac{100 \text{ per cent} - 6 \text{ per cent}^*}{100 \text{ per cent} - \text{PA per cent}}$$

The magnitude of twenty-five shunts was calculated from both O_2 [14,15] and Kr^{85} data and expressed as the ratio of pulmonary to systemic flow. These results are related in Figure 7. In general, there was fair correlation between the results by the two methods, although the Kr^{85} test usually indicated a lower ratio than did the O_2 method. This illustration also demonstrates that shunts resulting in pulmonary to systemic flow ratios as low as 1.1:1 could uniformly be detected with the Kr^{85} test. With the O_2 method, on the other hand, shunts of this magnitude could not be diagnosed with certainty as control patients had calculated ratios as high as 1.2:1.

* This formula must be modified in the presence of an associated right-to-left shunt. Under these circumstances the arterial Kr^{85} content is lower than that in shunted blood, and an assumed pulmonary venous content must be substituted for the arterial level in determining the $\frac{PA}{A}$ ratio.

COMMENTS

Both the oxygen and Kr^{85} methods for detecting left-to-right shunts are based upon a difference in gas content of arterial and venous blood. This arteriovenous difference, however, is established by different mechanisms. The oxygen content of venous blood is always lower than that of arterial blood because the tissues constantly remove oxygen. Any significant change in the patients' metabolic state may alter the arteriovenous oxygen difference, usually by changing the venous O_2 content. The arteriovenous difference in Kr^{85} content, on the other hand, is not a function of body metabolism, but of tissue absorption by physical solution of the gas. Once tissue saturation is achieved, the gas is no longer extracted from arterial blood, and the arteriovenous difference is obliterated. Thus, although Kr^{85} does not provide a continuous arteriovenous difference, it does provide a large and relatively constant one during the early period of inhalation. During this time the venous level bears a fixed relationship to the arterial level, the ratio always being under 15 per cent and usually under 10 per cent, between the tenth and thirtieth seconds. (Fig. 2.) Thus, it is not necessary to determine the Kr^{85} content of blood proximal to a shunt in order to detect its presence.

The errors in detecting left-to-right shunts with the method of measuring oxygen differences stem either from the fact that the oxygen content of venous blood proximal to the shunt changes with alterations in the metabolic state, or that the O_2 content of "mixed" venous blood from vena caval samples is often not representative, particularly because of the sampling of laminar streams. These difficulties are avoided in the Kr^{85} test by simultaneous sampling and by the elimination of the necessity of vena caval sampling.

Blood samples were obtained at various time intervals during Kr^{85} inhalation in order to ascertain which was the optimal one. Figures 3 and 4 demonstrate that although a few patients in the later sampling group had ratios between 10 and 20 per cent, the vast majority of them had tests in which results were clearly positive or negative. In over 90 per cent of the patients, the sampling time did not affect the diagnosis. However, in patients with left-to-right shunts, the timing of the samples was found to alter greatly the ratio itself, even though the diagnosis was not changed. Figure 2 demonstrates that the ratios of samples drawn beyond the shunt to the arterial samples changed from over 100 per cent at five seconds, to 70 per cent at fifteen seconds, and to 39 per cent at twenty-five seconds. This rapid change in the ratio was due to the fact that the rapidly rising Kr^{85} concentration in shunted (pulmonary venous) blood was not reflected immediately in peripheral arterial blood. As pulmonary venous blood approached saturation, usually within twenty seconds, and in children as early as ten seconds, this discrepancy disappeared and peripheral arterial blood was then representative of shunted blood.

In order to minimize the effects of the rapid change in the ratio at the beginning of inhalation, it would appear that the samples should be drawn after twenty seconds of inhalation. However, by this time the Kr^{85} concentration of returning venous blood in many patients is increasing, and may contribute to the ratio distal to the shunt. Thus, no single period for sampling is optimal in all patients and it was found necessary to select one which represented a satisfactory compromise, applicable in most persons. The integrated samples drawn between the tenth and thirtieth seconds of inhalation were found to be adequate for both the detection of a shunt and an estimate of its magnitude, and are now used routinely. Occasionally, the results of a test may be inconclusive (between 10 and 20 per cent). Under these circumstances the test is repeated with samples drawn between the tenth and fifteenth seconds. If the patient does not have a shunt, the earlier sampling period will uniformly result in a ratio well under 10 per cent, as in the control patients of Figure 3. If the patient has a left-to-right shunt, the resulting ratio will always be higher, as illustrated in Figure 2. Thus, during the early seconds of inhalation the Kr^{85} ratio may be quite large, even in the presence of a small shunt. This feature of the test makes it of particular value in the detection of very small shunts which may remain otherwise unrecognized.

The magnitude of a left-to-right shunt as calculated from oxygen data has long been recognized to be only an estimation [*14,15*]. Similarly, the magnitude of such a shunt as determined from the Kr^{85} ratio must also be regarded as only an estimate, since the Kr^{85} determinations represent only an average of the changing concentrations during the sampling period. For purposes of clinical evaluation of the magnitude of a shunt,

the results of Kr^{85} tests may be conveniently classified in a manner similar to that described for N_2O [*2*]. Ratios of 20 to 40 per cent are associated with small shunts; ratios between 40 and 60 per cent are indicative of moderate sized shunts with pulmonary flows equal to 1.5 to 2.5 times systemic flows; and ratios exceeding 60 per cent are seen with large shunts. Studies recently made in experimental animals, in which pulmonary and systemic flows were metered, indicated that the application of the mixing formula for inert gases such as Kr^{85} and N_2O is valid, and that the above ratios correlate well with shunts of the magnitudes described [*16*].

Since only 0.6 per cent of the emissions of Kr^{85} are gamma rays, very low counts are obtained from samples placed in a scintillation detector. Some variety of Geiger-Müller tube is therefore necessary to assay the isotope in blood with the doses used. The method for extracting Kr^{85} from the blood was originally devised to produce maximum counting efficiency. However, it was later found that a continuous gas flow tube was capable of counting Kr^{85} in whole blood without too great a loss of efficiency. Furthermore, this tube has proved to be more convenient and less fragile than the end-window type of Geiger-Müller tube. When duplicate samples were counted the whole blood technic gave more reproducible results than the extraction method and its accuracy approximated that of the manometric analysis for N_2O. (Fig. 5.) A tube with a 10 cc. capacity was first used, but more recently has been replaced with one of 3.5 cc. capacity. When the ten to thirty second sampling period is employed, 4 or 5 cc. of blood is usually obtained and the counting chamber may be filled without dilution of the sample. In counting whole blood it is important that contact of the sample with air be minimized since Kr^{85} is far more soluble in air than water. The background count must be checked after each sample is washed from the tube, and to minimize the effects of changes in background upon the results, the arterial level should exceed 100 counts per minute (when the background count is near 20).

Other radioactive inert gases have been used experimentally for the detection of intracardiac left-to-right shunts. Ethyl iodide, containing I^{131}, has been investigated by Case et al. [*17*], and trifluoriododomethane, also containing I^{131}, has been evaluated in this laboratory. Although the results with these gases were similar to those obtained with Kr^{85}, the eight-day half-life of I^{131} requires supplies of gases containing it to be replenished at frequent intervals. Kr^{85} was selected for the present study because its long half-life of about ten years permits storage of the gas indefinitely. This long physical half-life, however, does not increase the hazard to the patient, as it is an inert gas and is rapidly and completely excreted from the body through the lungs. Thus, the biological half-life of Kr^{85} is only a few minutes. The total amount of radiation received by the patient is many times less than that received from the fluoroscope when the catheter is being positioned. Additional radiation safety precautions are necessary in the handling and administration of a radioactive gas. Since some air contamination always occurs, the laboratory should be well ventilated and the use of a monitor in the room is desirable. The major source of hazard is escape into the room of large quantities of gas from the storage cylinder. The cylinder should be kept in a hood except when in actual use, and its fittings and reducing valve carefully and frequently checked for leaks.

Kr^{85} has other diagnostic uses. Lassen and Monck first used this gas in the determination of cerebral blood flow [*18*], and it may be used in a similar way for the determination of renal and coronary blood flow. The fact that Kr^{85} is rapidly excreted through the lungs has suggested its use in determining pulmonary diffusion [*19*]. Although it is poorly soluble in water, Kr^{85} can be dissolved in fluid and injected intravenously. This technic is currently being investigated as a means of detecting right-to-left shunts.

SUMMARY

A method for the detection, localization, and quantification of left-to-right circulatory shunts by the inhalation of an inert radioactive gas, Kr^{85}, is described. In the course of cardiac catheterization patients inhaled the gas for thirty seconds as integrated blood samples were drawn simultaneously from a systemic artery and a right heart chamber or the pulmonary artery. Fifty-six Kr^{85} tests were performed in forty-five patients without left-to-right shunts. Among these control tests the radioactivity of the pulmonary arterial or right heart sample was always less than 15 per cent of that in the arterial sample. Of the sixty-nine tests performed in patients with proved shunts the ratio exceeded 20 per cent in all but six instances, when it was between 15 and 20 per cent. The magnitude of the shunt could also be estimated by comparing pulmonary and

systemic arteriovenous differences in Kr^{85} content.

In all patients N_2O tests were performed in the same chambers in which Kr^{85} tests were performed, and in all patients with shunts determinations of blood oxygen content were also made. The results of the Kr^{85} tests were comparable in every instance to those of the N_2O tests and both were superior in diagnostic accuracy to the oxygen method. With the Kr^{85} test, shunts resulting in pulmonary to systemic flow ratios of 1.1:1 could uniformly be detected. The Kr^{85} content of blood samples was determined with a Geiger counter and the results of the test were available within a few minutes. The Kr^{85} test thus combines the accuracy of the N_2O test with a simple and rapid technic of analysis.

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Pulmonary Artery Stenosis*

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IN the past several years a number of cases of stenosis of one or both main branches of the pulmonary artery have been reported in the medical literature [*1–13*]. In some instances the stenosis has been an unexpected finding at thoracotomy [*1,3,11*]. The diagnosis in other cases has been made or suggested by angiocardiogram and/or catheterization of the right side of the heart. Stenosis of a branch of the pulmonary artery is likely when there is a persistent pressure gradient from a proximal to a more distal portion of the pulmonary artery.

Stenoses have been reported as isolated lesions in the main pulmonary artery, in its major branches, and in peripheral branches only. Infundibular or valvular pulmonic stenosis, ventricular septal defect, atrial septal defect, anomalously draining pulmonary veins, patent ductus arteriosus or a combination of some of these lesions may be associated.

We have made the diagnosis of pulmonary artery stenosis in five patients within the last eighteen months. Two had no other apparent lesions of the heart or great vessels; three had evidence, by catheterization of the right side of the heart, of ventricular septal defect, probable common atrioventricular canal, and patent ductus arteriosus, respectively. None had pulmonic valve stenosis. The purpose of this paper is to present case reports of these five patients, to discuss the incidence and diagnosis of pulmonary artery stenosis, to determine whether or not there are any useful clues for the clinical diagnosis, and to consider the etiology and physiologic significance of narrowing of the pulmonary artery or its main branches.

CASE REPORTS

CASE 1. A seven year old girl came to the Pediatrics Clinic in January 1954 at age four. Her mother had had rubella during the first trimester of pregnancy. When the child was six months old a cardiac murmur was first reported to the parents. Development had been normal. There had never been any restriction of activity because of dyspnea or fatigue.

She was thin and, except for a cataract in the left eye and a cardiac murmur, the physical examination was within normal limits. The pulse was 88/minute and the blood pressure was 120/70 mm. Hg (right arm) and 150/80 mm. Hg (right leg). The heart was not enlarged. The basal second heart sound was loudest to the left of the sternum. There was a moderately loud harsh systolic murmur, loudest in the second right intercostal space to the right of the sternum. The murmur was also heard in the neck and back and to the left of the sternum.

Hemogram and urinalysis were normal. The electrocardiogram was within normal limits. On fluoroscopy, the main pulmonary artery appeared moderately prominent, but no definite ventricular enlargement was noted.

A diagnosis of congenital heart disease was made but the nature of the lesion was not clear. Because of lack of symptoms, and normal x-ray films and electrocardiogram, further studies were not carried out at that time. In June 1955, she experienced a possible mild convulsive seizure at home. During this seizure she appeared cyanotic for the only time. She gained weight and continued to do well. In July 1956, however, her mother reported that the child appeared to be tiring easily.

She was admitted to the hospital on August 27, 1956, for catheterization of the right side of the heart. The blood pressure in the left arm was 110/62; in the right, 114/40-0 mm. Hg. Cardiac sounds were the same as previously described.

On August 29, 1956, catheterization of the right side of the heart (Table 1) demonstrated a persistent pressure gradient near the origin of the right pulmonary artery (Fig. 1), indicating stenosis at this region. The catheter distal to this region was not wedged and the tip was well within the mediastinal border. Despite several attempts the catheter was not passed into the left pulmonary artery. Intracardiac pressures were normal and no shunts were demonstrated. It was not possible to obtain an undamped pressure pulse tracing from the right brachial artery. By sphygmomanometer, the blood pressure in the right arm was 104/52-40 mm. Hg. An angiocardiogram (Fig. 2) a few days later confirmed the presence of stenosis of the

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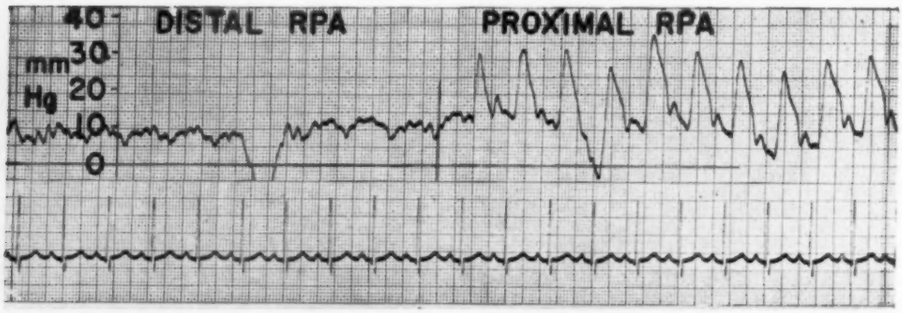

FIG. 1. Case I. Continuous pressure tracing as catheter was withdrawn from distal to proximal right pulmonary artery. Note the abrupt rise in pressure, indicating stenosis of the right pulmonary artery. Blood samples obtained distal to and proximal to the stenosis had the same oxygen content. Fluoroscopically, the catheter was not "wedged" in the distal pulmonary artery.

right pulmonary artery near its origin. The left pulmonary artery appeared normal although it was not seen in entirely satisfactory projection.

No specific therapy was recommended. The child, seen periodically in the Pediatrics Clinic, has been well. Electrocardiograms and chest roentgenograms have shown no significant changes.

Comment: Although aortic stenosis or other left-sided cardiac lesions have not been eliminated as possible explanations of the murmur, there is no clinical evidence to support such a diagnosis. The findings are consistent with stenosis of the right pulmonary artery near its origin. The cause of the wide pulse pressure in the right arm is not clear. Normal total pulmonary resistance suggests that the lesion is not causing a large elevation of right ventricular work, at least with the patient at rest.

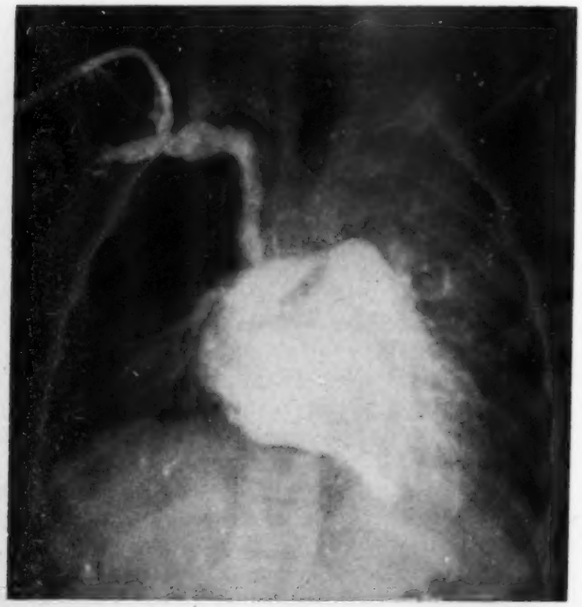

FIG. 2. Case I. Venous angiocardiogram clearly demonstrating narrowing of the right pulmonary artery near its origin. The left pulmonary artery is not well seen. The darker appearance of the right lung field is artifactual since the entire left half of the film was lighter than the right due to technical error.

CASE II. A six year old girl was first admitted to the hospital on August 23, 1956. A cardiac murmur had been heard when she was three years old. She had had several episodes of "tonsillitis." In February 1956, measles was followed by sore throat and fever for which she was given penicillin. In April she had fever and hot, red swollen knees. She was at bedrest a month and was treated with salicylates. In July, fever reappeared and her right elbow became swollen, painful and red. Penicillin and corticosteroids were given for two weeks. Cyanosis had never been observed. Her growth and development had been normal. She had not been dyspneic or easily fatigued.

She did not appear ill. The pulse was 100/minute, and the blood pressure was 115/60 mm. Hg (right arm) and 125/70 mm. Hg (right leg). The tonsils were large but not inflamed. Dental caries was present. Several moderately large anterior cervical lymph nodes were present. Except for the heart, the remainder of the physical examination was within nor-

TABLE I
CATHETERIZATION FINDINGS IN CASE I

Site	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)
Superior vena cava	8.6	.....
Inferior vena cava	10.4*	.....
Right atrium	10.0*	(2)†
Right ventricle	9.6*	29/2
Main pulmonary artery	9.4*	26/8 (17)
Proximal right pulmonary artery	9.8	31/9 (17)
Distal right pulmonary artery	9.9	9/6 (7)
Right brachial artery	14.1	.....
Arterial oxygen saturation	96%	.....

* Indicates the mean of two or more samples.
† Figures in parentheses represent mean pressures.

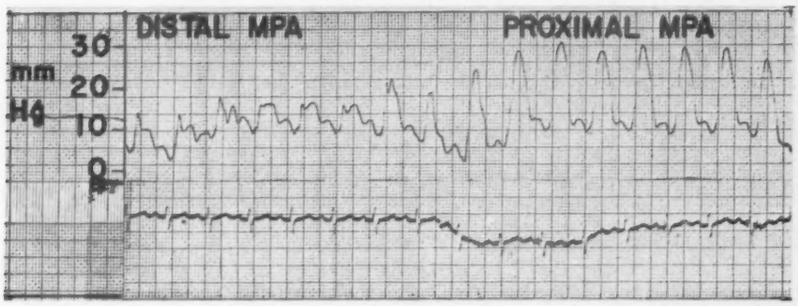

FIG. 3. Case II. Continuous pressure tracing as catheter was withdrawn from distal to proximal segment of the main pulmonary artery. The sudden rise in pressure indicates stenosis of the main pulmonary artery. Pressure in both major pulmonary artery branches was the same as in distal segment of main pulmonary artery.

mal limits. The heart was not enlarged. The second heart sound at the base was normally split and loudest to the left of the sternum. A moderately loud, rather harsh systolic murmur was heard best in the second right interspace at the right sternal border. A higher-pitched systolic murmur was heard along the left sternal border and at the apex. Continuous with the basal systolic murmur was a low-pitched rumbling diastolic murmur, heard best with the patient sitting, and more faintly when she was lying down. This murmur was not obliterated by compression of the neck veins.

Hemogram and urinalysis were normal. Erythrocyte sedimentation rate (Wintrobe) was 32 mm. and 29 mm. Throat culture contained no beta-hemolytic streptococci. Antistreptolysin O titer was 500 units. Sheep cell agglutination test was negative. No L.E. cells were found. Electrocardiogram showed rsR′ in leads V4R and V3R and RSr′ in lead V1. Cardiac fluoroscopy was normal. Roentgenograms of the elbows and knees were normal.

It was thought she had had acute rheumatic fever and congenital heart disease, probably a small patent ductus arteriosus. After a week in the hospital, she was discharged. Prophylactic benzathine penicillin was prescribed.

She was readmitted on May 29, 1957, for catheterization of the right side of the heart. In the interval she had been well. Findings on examination of the heart were unchanged. There was no evidence of rheumatic activity. At cardiac catheterization on May 31, 1957 (Table II) there was a persistent pressure gradient between the proximal and distal segments of the main pulmonary artery. This was demonstrated twice as the catheter was withdrawn from the distal segment of the main pulmonary artery. (Fig. 3.) There was no evidence of pulmonic valvular stenosis. Systolic pressures in the proximal pulmonary artery and right ventricle were slightly higher than normal. Other pressures were normal and there was no evidence of intracardiac shunt.

It was believed that there was insufficient indication for surgery, and the child is being seen periodically in the outpatient clinic.

TABLE II
CATHETERIZATION FINDINGS IN CASE II

Site	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)
Superior vena cava	11.5	.....
Inferior vena cava	12.2	.....
Right atrium	11.8*	(2)†
Right ventricle	11.8*	36/3
Proximal main pulmonary artery	....	32/9 (17)
Distal main pulmonary artery	11.7	15/8 (11)
Right pulmonary artery	11.7	15/7 (11)
Left pulmonary artery	11.6	15/7 (11)
Pulmonary artery wedge	....	(6)
Right brachial artery	16.0	.....
Arterial oxygen saturation	97%	106/80 (84)

* Indicates the mean of two or more samples.
† Figures in parentheses represent mean pressures.

Comment: This child has evidence of stenosis of the main pulmonary artery with no other apparent congenital defects of the heart or great vessels. Stenosis in this portion of the main pulmonary artery has been described by Kjellberg and associates [*4*] and corresponds to the "Type I" lesion described by Gyllenswärd et al. [*9*]. As in several of the patients reported by Eldridge, Selzer and Hultgren [*10*], a continuous murmur was present at the base of the heart. This led to an erroneous clinical diagnosis of patent ductus arteriosus.

CASE III. A four year old boy was brought to the Pediatrics Clinic on September 7, 1956. He had been born with ptosis of the left eyelid and asymmetry of the head. He had had frequent upper respiratory tract infections since infancy. When the child was two and a half years old his mother was told he had "heart valve disease." He had never been cyanotic or

TABLE III
CATHETERIZATION FINDINGS IN CASE III

Site	Preoperative 9/4/57		Postoperative 1/15/58	
	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)
Superior vena cava	11.4	.....	....	.....
Inferior vena cava	13.0	.....	....	.....
Right atrium	11.3*	(0)†	10.9*	(4)
Right ventricle	12.8*	60/2	11.0*	38/6
Main pulmonary artery	13.1	56/6 (26)	11.3	38/8 (21)
Right pulmonary artery	13.1	24/5 (12)	11.0	29/10 (18)
Left pulmonary artery	13.2*	27/8 (15)	10.9	29/8 (17)
Pulmonary artery wedge	....	(4)	....	(8)
Right femoral artery	14.3	.....	....	.....
Left brachial artery	....	.....	15.0	93/67 (78)
Arterial oxygen saturation	96%	.....	95%	.....

* Indicates the mean of two or more samples.
† Figures in parentheses represent mean pressures.

dyspneic. Development had been normal although he was underweight. When he was seventeen months old he had suffered an "infection" of the right eye which resulted in corneal scarring. At age three he had had otitis and mastoiditis.

The blood pressure was 74/52 mm. Hg in the arms, 122/52 mm. Hg in the legs. He was a small and thin boy with slight asymmetry of the occiput. The eyes revealed ptosis of the left lid and scarring of the right cornea. The lungs were clear. The heart did not appear enlarged, but the left anterior chest was slightly prominent. A systolic thrill was easily palpable in the third and fourth left intercostal spaces along the left sternal border. At this area there was a loud harsh systolic murmur, widely transmitted. The second heart sound was split and loudest at the base to the left of the sternum. Physical examination was otherwise within normal limits.

Hemogram and urinalysis were normal. Electrocardiogram showed right ventricular hypertrophy. Cardiac fluoroscopy demonstrated enlargement of both ventricles and prominent hilar and pulmonary vascular shadows.

When seen six months later, the child's mother reported that he had had three episodes of "asthma" with dyspnea, wheezing and cyanosis. Six months later, when he was admitted for cardiac catheterization, his mother had noted that he appeared not to keep up with his playmates, that he appeared dyspneic and had frequently been observed squatting. Physical examination was unchanged.

Catheterization of the right side of the heart on September 4, 1957 (Table III) demonstrated a left-to-right shunt at the ventricular level amounting to about 125 per cent systemic flow, moderate pulmonary hypertension and persistent pressure gradients at the origin of both main right and left pulmonary arteries. (Fig. 4.)

At surgery on October 4, 1957, using a pump-oxygenator, a ventricular septal defect was repaired by Dr. Ormand C. Julian. For technical reasons, the pulmonary artery was not explored for the presence of stenosis.

The patient was readmitted to the hospital for catheterization of the right side of the heart, on January 13, 1958. He had been well postoperatively with a decrease in dyspnea. Moderately loud low-pitched systolic murmurs were now audible in the second and third intercostal spaces bilaterally about 2 cm. lateral to the sternal borders. There was a soft systolic murmur at the apex and along the left sternal border. Roentgenograms of the chest showed no change in heart size or configuration. Catheterization of the right side of the heart was repeated on January 15, 1958. (Table III.) There was no evidence of an intracardiac shunt at the ventricular level, indicating that the ventricular septal defect had been successfully closed. Although smaller in magnitude, pressure gradients at the origins of both main right and left pulmonary arteries persisted.

Comment: There is evidence, from cardiac catheterization, of stenosis at the origin of both main pulmonary artery branches. Unfortunately, this region could not be investigated at surgery. Postoperatively, even at rest, main pulmonary artery and right ventricular systolic pressures are mildly elevated. The normal pulmonary artery pressures beyond the stenosis

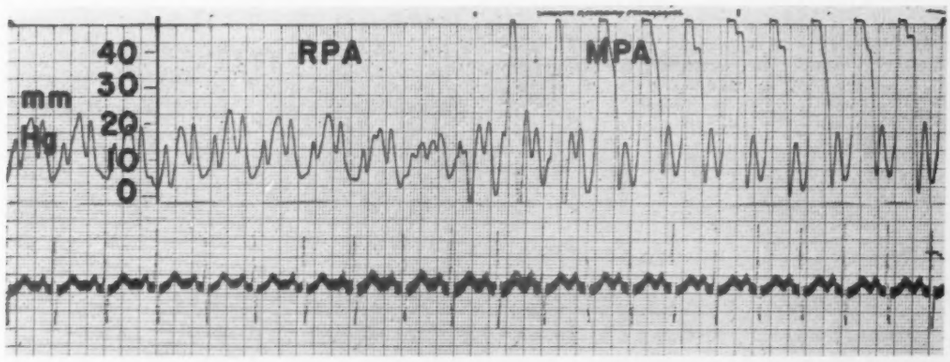

FIG. 4. Case III. Abrupt pressure rise as catheter was withdrawn from right to main pulmonary artery, pointing to stenosis at the origin of the right pulmonary artery. A similar rise was noted as the catheter was pulled from the left to the main pulmonary artery. After repair of the ventricular septal defect, these pressure gradients, although less in magnitude, persisted.

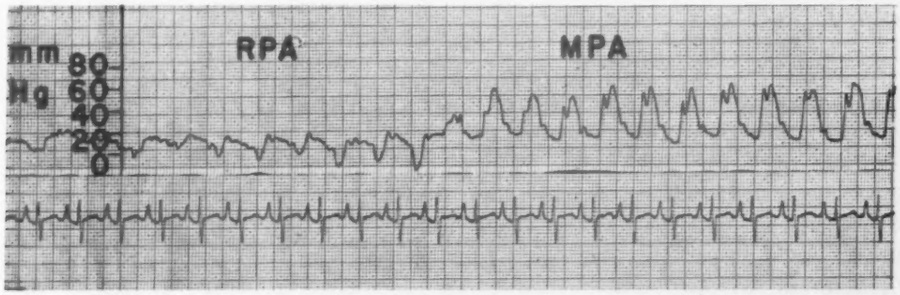

FIG. 5. Case IV. Continuous pressure tracing during withdrawal of catheter from right to main pulmonary artery, demonstrating sudden rise in pressure, indicating stenosis at origin of right pulmonary artery. Catheter could not be advanced into left pulmonary artery.

indicate that pulmonary vascular resistance is normal. The elevated main pulmonary artery and right ventricular systolic pressures are therefore probably due to resistance offered by the stenotic pulmonary arteries.

CASE IV. A ten months old female infant was brought to the Pediatrics Clinic in June 1957. A cardiac murmur had first been detected when the infant had "pneumonia" at age four months. Four months later there was another episode of "pneumonia." Except for somewhat slow physical development and weight gain, the child had been well. There was no cyanosis.

On examination, there was a left precordial bulge. The cardiac rhythm was regular. The second heart sound was widely split and very loud at the base to the left of the sternum. The following murmurs were heard: (1) moderately loud high-pitched basal systolic; (2) loud lower-pitched systolic along left sternal border, heard well at the cardiac apex and in back; and (3) apical low-pitched diastolic murmur. Examination was otherwise within normal limits. Electrocardiogram showed evidence of right ventricular hypertrophy of the diastolic overloading type, left axis deviation (−90°) and large P waves. Chest roentgenograms showed cardiomegaly to which both ventricles contributed, a prominent main pulmonary artery and prominent pulmonary vascular shadows. Hemogram and urinalysis were normal.

TABLE IV
CATHETERIZATION FINDINGS IN CASE IV

Site	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)
Superior vena cava	9.1	.....
Inferior vena cava	9.6	.....
Right atrium	10.8*	(3)†
Right ventricle	12.1*	60/1
Main pulmonary artery	12.2	51/12 (30)
Right pulmonary artery	12.4	19/9 (14)
Left atrium	14.4	(6)
Left superior pulmonary vein	14.5	.....
Right femoral artery	14.6	88/58 (74)
Arterial oxygen saturation	96%	.....

* Indicates the mean of two or more samples.
† Figures in parentheses represent mean pressures.

Catheterization of the right side of the heart on September 11, 1957 (Table IV) revealed a left-to-right intracardiac shunt at the ventricular level and possibly at the atrial level, atrial septal defect or patent foramen ovale, pulmonary hypertension, a small pressure gradient across the pulmonic valve and a large pressure gradient at the origin of the right pulmonary artery. (Fig. 5.) The left pulmonary artery could not be catheterized.

TABLE V
CATHETERIZATION FINDINGS IN CASE V

Site	Oxygen Content (ml./100 ml.)	Pressure S/D (mm. Hg)
Superior vena cava	8.9*	.....
Right atrium	8.8*	(0)†
Right ventricle	8.6*	43/3
Main pulmonary artery	12.4	43/22 (34)
Right pulmonary artery	12.5	30/21 (26)
Left pulmonary artery	12.5	31/20 (23)
Aorta	14.2	112/43 (73)
Aortic oxygen saturation	96%	.....

* Indicates the mean of two or more samples.
† Figures in parentheses represent mean pressures.

It was decided to delay surgery until the child is older and the surgical risk lessens.

Comment: An atrial septal defect or patent foramen ovale was detected by passing the catheter from the right atrium to the left atrium and left pulmonary vein. The presence of atrial and ventricular septal defect, together with the physical and electrocardiographic findings, suggest the presence of common atrioventricular canal. Mild pulmonic valvular stenosis may be present. Pulmonary blood flow is more than twice systemic blood flow. One cannot be certain that stenosis of the left pulmonary artery exists, but this appears quite likely in the absence of striking disparity in the vascularity of the two lungs as demonstrated by x-ray studies.

CASE V. A five year old boy first visited the Pediatrics Clinic on May 24, 1957. A cardiac murmur had been detected when he was one year old. Except for a congenital, poorly developed right eye and a bout of "pneumonia" at one year of age, growth and development had been normal. He had never been cyanotic or dyspneic.

The blood pressure was 130/60 mm. Hg in the arms, 160/70 mm. Hg in the legs. The heart was not enlarged and cardiac rhythm was regular. A continuous murmur, typical of patent ductus arteriosus, was present at the base. Along the left sternal border in the third and fourth intercostal spaces there was a high-pitched blowing early diastolic decrescendo murmur. Except for the findings in the right eye, the remainder of the physical examination was not unusual.

Hemogram and urinalysis were normal. Electrocardiogram showed good evidence of left ventricular hypertrophy. Cardiac fluoroscopy revealed left ventricular enlargement, possibly some right ventricular enlargement and prominent pulmonary vascular shadows.

At catheterization of the right side of the heart on September 20, 1957 (Table v) the catheter passed from the main pulmonary artery through a patent ductus arteriosus into the descending aorta. Persistent pressure gradients between the main pulmonary artery and both its branches were demonstrated. Right ventricular systolic and main pulmonary artery pressures were moderately elevated.

A few weeks later the patent ductus arteriosus was divided. Because of the surgical approach, only the left main pulmonary artery branch could be adequately seen and palpated. There was no external evidence of constriction nor was there a thrill at the origin of the left pulmonary artery. The artery was not explored. Three months postoperatively there was a moderately loud systolic murmur in the third left intercostal space about 2 to 3 cm. lateral to the sternal border and a separate higher-pitched softer systolic murmur in the second right intercostal space, a few centimeters lateral to the sternal border.

Comment: The failure to note external constriction of the left pulmonary artery or to feel a thrill at surgery casts some doubt on the diagnosis of stenosis of the pulmonary artery. The persistent pressure gradient, however, is not well explained by other mechanisms (*vide infra*).

COMMENTS

Incidence. Including this report, thirty-three patients with stenosis of a main branch of the pulmonary artery have been described [*1–3,5–7, 9–11,13,14*]. Others have been mentioned briefly [*4,8,10*] or reported in abstract form [*12*], bringing the total to well over fifty patients. Only three were reported prior to 1954 [*1,2,14*] when Sondergaard [*3*] described three patients who were found at surgery to have narrowing at the bifurcation of the main pulmonary artery.

In reviewing the autopsy files of the University of Illinois Research and Educational Hospitals from 1926 to the present we were unable to find a single report on a case of localized narrowing of the pulmonary artery or its major branches. Only one postmortem observation of this entity has been recorded [*14*]. The failure to find this lesion more frequently at autopsy is surprising in view of the routine dissection of the main pulmonary artery and its major branches in most hospitals and in view of the severe degree of narrowing required to produce a significant pressure gradient [*11*].

Diagnosis. Stenosis of a main branch of the pulmonary artery may be suspected from the physical examination, especially if other lesions are absent. Murmurs of septal defects, patent

ductus arteriosus and pulmonic stenosis, however, direct attention away from an associated pulmonary artery stenosis. Eldridge, Selzer and Hultgren [*10*] have indicated the importance of this lesion as a cause of continuous murmurs over the chest. One of our patients had a continuous murmur, not explained by other lesions. Systolic murmurs alone, however, are more frequent. These systolic murmurs are occasionally loudest in the second or third intercostal spaces several centimeters lateral to the sternal borders, as in our first, third and fifth patients. This is an unusual location for the murmurs of septal defects and aortic or pulmonic stenosis. Murmurs in these locations should, therefore, suggest the presence of pulmonary artery stenosis. Even when no other lesion is present, however, the murmur may be maximal at the base parasternally or occasionally at the apex.

The patient's history is not helpful in making the diagnosis.

Chest roentgenograms and fluoroscopy may show evidence of right ventricular enlargement. The main pulmonary artery segment may be normal or prominent. These signs likewise are not helpful. A central narrowing of the hilar vessels has been noted in some patients with pulmonary artery stenosis. Pulmonary vascularity may be increased, decreased or normal, depending on the hemodynamic effects of the stenosis and associated lesions.

In the absence of pulmonic stenosis, the electrocardiogram varies with the nature and extent of associated lesions and with the severity of right ventricular hypertension due to pulmonary artery narrowing. Evidence of right ventricular hypertrophy need not be present.

The diagnosis of stenosis of a main branch of the pulmonary artery can be made at the time of catheterization of the right side of the heart by the observation of an abrupt pressure rise as the catheter is withdrawn through the narrowed segment. As noted by Williams, Lange and Hecht [*11*], it is important to obtain blood samples distal to the stenosis to be certain that the pressure increase is not the result of withdrawal of the catheter from the pulmonary artery "wedge" position. Oxygen content of blood distal to the stenosis should therefore be the same as that proximal to it.

Despite no other apparent change in the "steady state" during catheterization of the right side of the heart, pulmonary artery pressure may vary significantly with the passage of time.

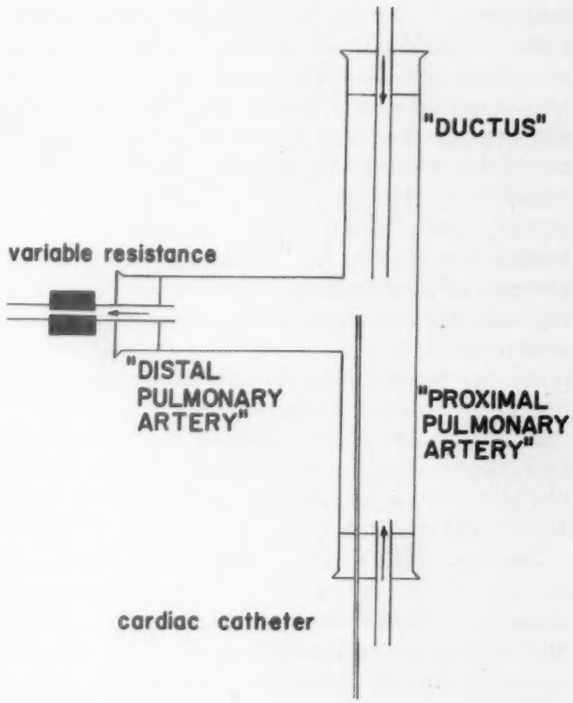

FIG. 6. Diagram of glass model described in text to investigate whether or not flow from "ductus" could produce pressure gradient between "proximal" and "distal pulmonary artery."

Diagnosis thus further requires that the pressure gradient be recorded during continuous withdrawal of the catheter.

It has been demonstrated that pressure in the pulmonary artery near a patent ductus arterosus may be higher than the pressure recorded distally or proximally to it [*15*]. This does not necessarily indicate pulmonary artery narrowing. In the absence of pulmonary artery stenosis, no instance has been reported in which pressure proximal to a patent ductus arteriosus was higher than that recorded distal to the ductus.

An attempt was made to determine whether or not the pressure gradient in our patient with patent ductus arteriosus might be an artifact resulting from the forceful stream of blood emanating from the ductus. A T-shaped glass model (Fig. 6) was constructed, simulating the proximal pulmonary artery, patent ductus arteriosus and distal pulmonary artery. Water was admitted through the "proximal pulmonary artery" and "ductus" in an approximate ratio of 1:2 and left the system through the "distal pulmonary artery" at a flow of about 5 L. per minute. Mean pressure in the system could be varied between 10 and 40 mm. Hg by altering a

resistance at the end of the "distal pulmonary artery." Intraluminal pressures were measured at various points with a cardiac catheter.

It was found that the mean pressure at the entrance of the "ductus" into the pulmonary artery was no more than 5 mm. Hg higher than elsewhere in the system and that "proximal pulmonary artery" and "distal pulmonary artery" pressures were identical. Thus it appears that the presence of a pressure gradient on withdrawal of the catheter from a position in the pulmonary artery distal to a patent ductus arteriosus to a point proximal to the ductus indicates actual pulmonary artery constriction.

Finally, the diagnosis can be confirmed by venous angiocardiography or, as shown by the Swedish authors [*5,9*], by selective angiocardiography.

Etiology. The etiology of stenosis of the pulmonary artery is unknown. Most previous authors have concluded that it is usually a congenital developmental lesion. One can present convincing evidence for this argument.

First, pulmonary artery stenosis frequently occurs with congenital anomalies of the cardiovascular system. In addition, non-cardiovascular developmental anomalies were reported in eight of thirty-three patients described. Of special interest is the occurrence of congenital abnormalities of the eyes. Three of our five patients and one reported by Gyllenswärd and his co-workers [*9*] showed such defects. Several authors [*16–18*] have commented on the frequent association of congenital ocular defects with congenital heart disease. *Second*, in some patients with no detected cardiac lesion other than pulmonary artery stenosis, murmurs were heard in infancy or early childhood and dyspnea or retarded development was noted.

The stenosis may occur in the main pulmonary artery but is more frequently observed at the origin of its two branches or more peripherally. This variation in location is evidence against Sondergaard's [*3*] proposal of congenital narrowing of the pulmonary artery by fibers extending from the ductus arteriosus.

Although pulmonary artery stenosis may in most patients originate as a developmental anomaly in fetal life, the possibility that it occasionally occurs as an acquired lesion at some time after birth must be examined. Some evidence suggests that either pulmonary artery thrombosis or "natural transformation" of the pulmonary artery resulting from prolonged rapid pulmonary blood flow may occasionally produce pulmonary artery stenosis.

Pulmonary artery occlusion, partial or complete, may result from massive thrombosis or embolization [*19–24*], sometimes with survival of the patient for months or years afterwards. These lesions, which may eventually undergo recanalization, generally occur in adults but have also been reported in children. All patients reported have demonstrated abundant signs and symptoms of cardiac or pulmonary disease so that, although one might compare them to persons with pulmonary artery stenosis with severe cardiac disease, they do not resemble our patients with mild disability or none at all.

Thrombosis may thus be implicated in the production of pulmonary artery stenosis. Since autopsy has been performed on only one patient [*14*] with this entity, it is evident that histological examination of the narrowed area in such patients may help to evaluate this etiological possibility.

The term "natural transformation" was used by Gasul and associates [*25*] in describing the right ventricular outflow tract narrowing which, developing gradually over a number of years, may reduce the left-to-right shunt in patients with ventricular septal defect. One may inquire whether or not the prolonged increase in pulmonary blood flow in other patients with left-to-right shunt may in time produce "natural transformation" of the pulmonary artery, i.e., pulmonary artery stenosis, with consequent lessening of the shunt. Rodbard's studies [*26–29*] in animals and in models supports this postulate. He showed that when vessels converged or diverged [*29*] their lumens were gradually narrowed by the formation of "intimal" cushions. A similar mechanism could result in narrowing of the pulmonary artery, especially in those patients with stenosis at the bifurcation of the main pulmonary artery. These lesions would be more likely to occur in patients with greatly increased blood flow due to left-to-right shunt.

It will be of interest to repeat catheterization of the right side of the heart after several years in our patient who had surgical repair of his ventricular septal defect. If the pressure gradient disappears, it will strengthen the argument for "natural transformation" as a cause of pulmonary artery narrowing in this patient.

Physiologic Significance. The significance of pulmonary artery stenosis depends upon the resistance it offers to right ventricular outflow.

Resistance mainly depends upon the physical characteristics of the narrowing, i.e., upon its length and lumen. Since exact length of the lesion is unknown, it is fruitless to attempt to calculate orifice size although, as Williams, Lange and Hecht [*11*] have pointed out, if the length is very short as in a membranous stenosis, the lumen must be a small fraction of normal in order to produce detectable pressure elevation.

Normally a decrease in pulmonary vascular resistance prevents pulmonary arterial pressure elevation when blood flow through the lungs is doubled or tripled either by exercise or left-to-right shunt. It is very likely that pulmonary artery stenosis diminishes this moderating effect. Thus a lesion causing only a small pressure gradient at rest may with exercise produce significant right ventricular hypertension. Our third patient, in whom the gradient across the stenosis decreased sharply after surgical abolishment of the left-to-right shunt, illustrates the affect on the pressure gradient of reducing the blood flow.

The resistance afforded by the stenosis at rest varies from patient to patient. In some patients, especially those with multiple peripheral pulmonary artery stenosis noted by the Swedish authors [*5,9*], it is sufficient to produce severe right ventricular hypertension.

Finally, in the presence of abnormal communications between the pulmonary and systemic circulations, pulmonary artery stenosis might cause cyanosis and hypoxia, especially at exercise, by increasing pulmonary resistance enough to cause right-to-left shunting of blood. No clear-cut instance of this effect has been reported, however.

Treatment. Up to the present only two attempts to repair pulmonary artery stenosis have been recorded [*1,11*]. There can be little doubt of the great technical difficulty involved in graft replacement of stenotic portions of any segment of the pulmonary artery. If the external diameter of the vessel at the point of narrowing were great enough, it might be possible, using extracorporeal circulation, to open the artery and incise or excise a membranous stenosis.

It may be that pulmonary artery stenosis associated with pulmonic valvular or infundibular stenosis together with ventricular septal defect should be dealt with when the associated lesions are repaired. When pulmonary artery stenosis occurs in patients with large left-to-right shunts, it seems prudent not to disturb the stenosis when repairing the shunt. The pressure gradient across the stenosis will be reduced postoperatively and the possibility exists, as already noted, that in time the narrowing will gradually disappear. In any event, complete catheterization and angiocardiographic studies should be completed before operation.

SUMMARY

Stenosis of the main pulmonary artery and of its major and more peripheral branches is now a well recognized entity. The occurrence of associated congenital cardiac lesions is frequent.

This report adds five patients with pulmonary artery stenosis to the twenty-eight previously described. A study of these patients and review of the literature reveals some helpful clues to the diagnosis, and raises important questions about the etiology, physiologic significance and treatment of this lesion.

The clinical diagnosis of pulmonary artery stenosis is frequently hampered by coexistent cardiovascular lesions. A continuous murmur should make one think of the diagnosis. The lesion more commonly produces a systolic murmur which may be heard with maximal intensity at the base of the heart several centimeters lateral to the sternal border.

Pulmonary artery pressure rises abruptly when the cardiac catheter is withdrawn through the narrowed segment. In the absence of pulmonary artery narrowing, patent ductus arteriosus probably does not produce such a pressure change. The appearance of a constantly narrowed pulmonary artery segment on angiocardiogram strengthens the diagnosis.

Pulmonary artery stenosis probably occurs in most cases as a congenital anomaly. Pulmonary artery thrombosis or "natural transformation" might result in acquired stenosis.

The significance of the lesion depends on the resistance it offers to right ventricular outflow. A narrowing which causes a small pressure gradient at rest may with exercise produce significant right ventricular hypertension.

In most patients, pulmonary artery stenosis does not cause serious hemodynamic abnormalities. If these are present, however, surgical repair may be possible and desirable.

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Differential Pulmonary Artery Occlusion in Patients with Chronic Pulmonary Disease*

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Previous reports on the application of temporary unilateral pulmonary artery occlusion in man as a useful clinical and investigative technic have presented some unexpected findings, particularly in patients with pulmonary disease [*1–3*]. It has been shown that pulmonary vascular resistance may be influenced by factors other than at the arteriolar level; for instance, increased intra-alveolar pressure. Several ingenious methods have been devised by others to gain some insight into the role of uneven ventilation-perfusion relationships in the lung, in laboratory animals and in man [*4,5–7*]. Significant deviation from the normal relationships, particularly in patients with pulmonary disease, may be responsible for considerable change in the level of arterial blood gases. Peripheral arterial oxygen content and hemoglobin saturation may be materially lowered by a decreased ventilation perfusion ratio, Va/Qc. It is the purpose of this communication to present hemodynamic studies in five patients with pulmonary disease who were subjected to temporary occlusion of both main branches of the pulmonary artery with particular reference to the effect of each maneuver on the vascular pressures and resistance, arterial blood gases, and the study of ventilation-perfusion relationships.

METHODS AND MATERIAL

In Table I are given the clinical features of the patients studied, the diagnosis and the standard ventilatory function tests. Cardiac catheterization was carried out in the usual manner, using a special triple lumen cardiac catheter with an inflatable cuff on the middle lumen [*2*]. The patients were in a resting postabsorptive state, and light sedation (usually secobarbital 0.1 gm.) was used. The catheter was maneuvered into either the right or left main pulmonary artery and control values were obtained. Under fluoroscopic control, unilateral pulmonary artery occlusion was then carried out by inflating the cuff, and, after a steady state had been reached (usually fifteen to twenty minutes), repeat studies were obtained. The cuff was then deflated, the catheter repositioned in the opposite pulmonary artery, and the studies repeated. Blood samples obtained via the cardiac catheter and from the brachial or femoral artery were analyzed spectrophotometrically by the method of Hickam and Fraser [*8*] with duplicate analyses by the manometric method of Van Slyke [*9*]. Arterial blood oxygen tensions were determined by the bubble method of Riley [*10*]. Oxygen consumption was determined on room air by collection in a Douglas bag and analysis on a Beckman-Pauling oxygen analyzer. Arterial blood samples and pressures were obtained via an indwelling needle in the brachial artery. Although the patients were in a resting steady state, they were not necessarily "basal."

CASE HISTORIES

Case I. F. L., a sixty year old white man with a twelve-year history of chronic productive cough and postnasal drip, was found to have infiltrate of the upper lobe of the left lung on routine chest roentgenogram.

Physical examination revealed a thin, well developed, white man with an increased anteroposterior diameter of chest. Breath sounds were well heard throughout and there were no adventitious sounds. The hemoglobin was 15.2 gm. per cent and the hematocrit 51. Anteroposterior and lateral laminograms revealed an infiltrating lesion in the upper left lobe without evidence of cavitation, calcification or compression of tracheobronchial tree. A bronchial biopsy specimen and aspirates did not reveal any malignant cells. Pulmonary function studies and differential pulmonary artery occlusion showed that the patient could not tolerate pulmonary resection; he was discharged with a diagnosis of diffuse pulmonary emphysema and fibrosis with probable neoplasm of the lung.

Case II. T. B., a forty year old white man who had had bronchial asthma since childhood, was admitted

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TABLE 1

PATIENTS STUDIED: DIAGNOSIS AND PULMONARY FUNCTION RESULTS

Patient and Age (yr.)	Diagnosis	Height (inches)	Weight (pounds)	Surface Area (square meters)	Vital Capacity (L. and % of predicted normal)	Maximum Breathing Capacity (L. and % of predicted normal)	Timed Vital Capacity
F. L., 60.....	Carcinoma upper left lobe; chronic emphysema	71	147	1.84	2.3 (55%)	54 (53%)	1 second 49% Total time 8 seconds
T. B., 59.....	Carcinoma lower left lobe; chronic emphysema	59½	123	1.70	3.3 (78%)	81.5 (73%)	1 second 55% Total time 4 seconds
L. S., 54.....	Pulmonary fibrosis diffuse	69	142	1.80	4.1 (81%)	83.7 (80%)	1 second 36.4% Total time 8 seconds
L. D., 49.....	Bullous emphysema	67	130	1.68	1.6 (38%)	39 (38%)	1 second 51% Total time 6 seconds
C. K., 36.....	Extensive pulmonary tuberculosis left lung	73	174	1.76	3.0 (59%)	55 (33%)	1 second 63% Total time 5 seconds

because of the presence of unresolving infiltrate in the lower lobe of the left lung, anorexia and a 20 pound weight loss in six months.

Physical examination revealed a thin, emaciated white man who appeared chronically ill with an increased anteroposterior diameter of the chest. Breath sounds were distant with prolonged expiratory phase and wheezing throughout both lung fields. Decreased resonance and coarse rales were noted in the left infrascapular region posterolaterally. There was no cyanosis, clubbing or dependent edema. Hemoglobin was 11.8 gm. per cent and hematocrit 46. Chest roentgenograms showed pleuritis at the right apical area and a homogeneous density in the lower left lobe with an associated pleuritis and elevation of left leaf of diaphragm. Bronchial biopsy specimen obtained from the lower left lobe and bronchial aspirates revealed malignant cells. Pulmonary function tests and catheterization data indicated that the patient could tolerate surgery. Left pneumonectomy was performed and the patient was discharged on the eleventh postoperative day after an uneventful course.

CASE III. L. S., a fifty-four year old white man, had a two-year history of progressive exertional dyspnea and a chronic non-productive cough which was more severe on arising in the morning.

Physical examination revealed a well nourished, well developed white man with a plethoric facies and slight cyanosis of lips, fingers and toes. Lung fields were hyperresonant throughout and breath sounds were diminished and distant. There was clubbing of fingers and toes. The hemoglobin was 20.5 gm. per cent, hematocrit 61 and red blood cells 6.71 million per cu. mm. Chest roentgenograms revealed some cardiac enlargement with general and focal emphysema. Bronchograms showed evidence of bronchiectatic change in the middle and posterior portions of both lower lobes. An electrocardiogram showed right ventricular hypertrophy. A biopsy specimen taken from the right lung revealed bullous emphysema. The patient was treated symptomatically and discharged after completion of diagnostic studies.

CASE IV. L. D., a fifty year old Negro man, was admitted because of marked exertional dyspnea which had been present for five years and edema of the ankles which had been present for several weeks. Onset of symptoms had occurred suddenly, five years prior to admission, while lifting a heavy object. The

patient was taken to another hospital where a right thoracotomy was performed for tension pneumothorax. He was discharged after five weeks but continued to have exertional dyspnea.

Physical examination revealed a well developed, well nourished, Negro man. The lung fields were hyperresonant, with increased vocal fremitus and distant breath sounds. There was prolongation of expiratory phase and occasional scattered expiratory wheezes. Slight pretibial pitting edema was present. The hemoglobin was 13.4 gm. per cent and hematocrit 43. Venous pressure was 25 mm. of water and arm-to-tongue circulation time (Decholin®) was twenty-five seconds. Chest roentgenograms showed giant emphysematous blebs replacing the upper two-thirds of the right and the upper one-third of the left lung fields, and low diaphragms. An electrocardiogram was consistent with right ventricular hypertrophy. After completion of pulmonary function studies, the patient was taken to surgery for excision of bullae, wedge resections of the upper and lower lobes of the right lung and plumbage thoracoplasty. One year later excision of bullae and cysts, and plumbage thoracoplasty was performed on the left side. Subsequently considerable clinical and physiologic improvement was noted.

CASE V. C. K., a thirty-six year old white man, had a twenty-year history of pulmonary tuberculosis when admitted. In 1955, marked progression of the disease was noted. On admission the patient appeared chronically ill and examination of the chest revealed bronchial breathing over the upper posterior part and upper left anterior part of the chest with occasional crepitant rales. Chest roentgenograms showed bilateral apical disease with massive cavitation on the left extending from the apex down to the mid-lung field, and dense pneumonic disease in the apex.

After twenty-four months of therapy with resultant arrest and clearing of the disease on the right side, the patient was referred for surgical evaluation because of the massive cavity and persistent positive sputum. On the basis of the results of unilateral pulmonary artery occlusion studies, surgery was recommended. A left plumbage thoracoplasty was performed; and the patient tolerated surgery well. Sputum cultures have since been negative and patient is doing well.

RESULTS

In Table II are the pertinent data obtained. The salient features are plotted in Figure 1. Bilateral occlusion was carried out with little difficulty to the patient in all but Case V; in this case, the degree of pulmonary disease was so great as to preclude occlusion of the right pulmonary artery for a long enough period to permit complete studies. (Fig. 2.)

Arterial oxygen saturation, prior to occlusion, was significantly reduced below normal in all patients but C. K. (Case V). In L. S. (Case III) a secondary polycythemia was present. In T. B. (Case II) and C. K. (Case V), with lesions of the left lung, occlusion of the left pulmonary artery resulted in a definite increase in arterial oxygen saturation; however, in T. B. (Case II), when the right pulmonary artery was occluded, there was a fall below the control level. In patient F. L. (Case I), despite the presence of an isolated lesion of the upper left lobe, and in patients L. S. (Case III) and L. D. (Case IV), all with diffuse pulmonary disease, occlusion of first one and then the other pulmonary artery branches produced a variable decrease in oxygen saturation. This change was apparently dependent on the relative pathologic involvement of the two lungs.

Cardiac index showed little change during the course of the procedure, however, it appears that in Cases III, IV and V, the cardiac output closely paralleled the changes in arterial blood saturation, i.e., rising in response to a fall in hemoglobin saturation and falling when saturation rose. As has been previously demonstrated, little change in cardiac output occurs when unilateral pulmonary artery occlusion is carried out [*2,3*].

Oxygen consumption showed no significant changes despite the fact that, with occlusion of the pulmonary artery to one lung, all gas exchange was performed in the unoccluded lung.

Respiratory minute volume and tidal volume also showed no significant change. It should be emphasized that with occlusion of a pulmonary artery, the occluded lung continues to ventilate but there is no exchange. The unoccluded lung receiving the entire cardiac output now assumes the burden of all gas exchange with only a slight increase in alveolar ventilation. The ventilation/blood flow ratio (Va/Qc) then becomes infinity on the side of occlusion and one-half the control level on the unoccluded side. No striking hyperventilation occurred in response to this stimulus.

Pulmonary artery pressure, at rest, was moderately elevated in each case. Respiratory variation was marked and both peak inspiratory and expiratory values are given in all but Case IV, together with an over-all mean value. In no case was there an actual fall in pressure following occlusion of a main pulmonary artery branch as has been observed previously in several cases [*3*]. However, in Cases II and V there was only a slight increase when the extensively diseased lung was occluded. In these same cases a very sharp rise in pressure was observed when the more normal lung was

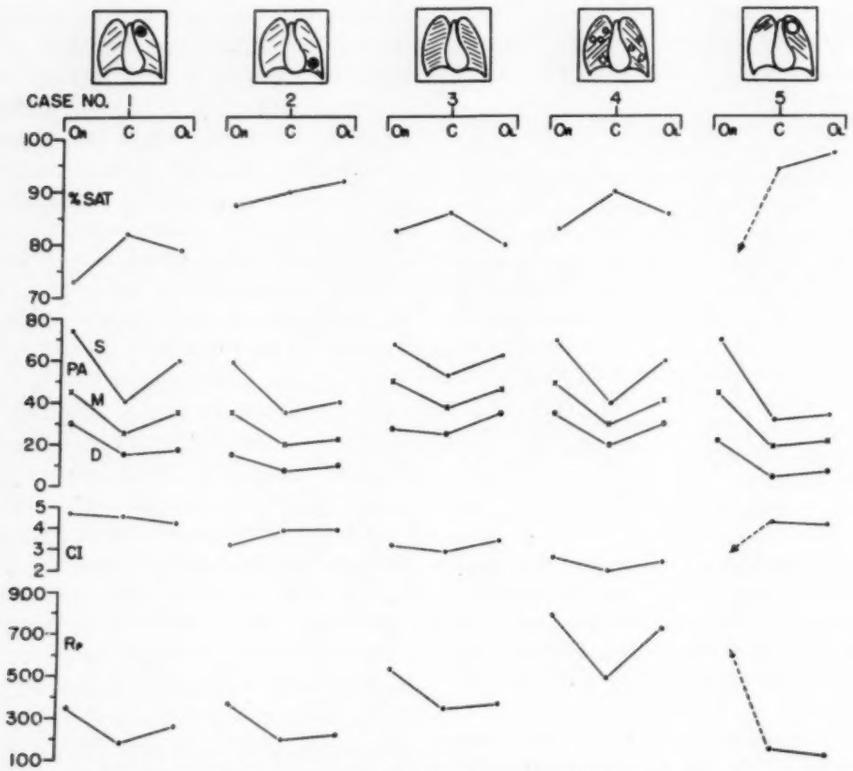

FIG. 1. Salient hemodynamic data for the five cases are plotted. C = control valves. O_R = occlusion of right pulmonary artery. O_L = occlusion of left pulmonary artery. Schematic representation of the disease present is given at the top for each case. Blank areas represent normal lung, shaded areas represent emphysema, and circled areas represent cysts in Case IV and cavities in Case V. Solid areas are tumors. From top to bottom are: per cent saturation of the arterial blood; pulmonary artery pressure, in mm. Hg, S = systolic, M = mean, and D = diastolic; cardiac index, in L./min./M^2; total pulmonary resistance in dyne sec. cm^{-5}. In Case V, because of the severe reaction, complete data following occlusion of the right lung were unobtainable, and the direction of changes are estimated by broken lines.

FIG. 2. Case V. Chest roentgenogram.

occluded, and in Case V rapid deflation was necessary before a steady state could be reached.

There is apparently a close relationship between the changes in arterial oxygen saturation and pulmonary artery pressure. This is most likely due to the associated increase in cardiac output with a fall in arterial oxygen saturation as well as the ability of the unoccluded lung to assume the entire cardiac output. The slight pressure increases observed in Cases II and V are considered normal while the others are considered abnormal. Both the pulmonary artery pressure response and arterial blood oxygen changes following occlusion may be considered good indices of the function of the unoccluded lung.

Right ventricular end diastolic pressures and right atrial pressures were normal.

Brachial artery pressures showed no change except in C. K. (Case V). With occlusion of the pulmonary artery of the normal lung in this patient there was a sharp fall in systemic pressure.

TABLE II

CARDIAC CATHETERIZATION DATA

	O_2 Capacity (Vol. %)	Arterial O_2 Content (Vol %)	Arterial Saturation (%)	Arterial pO_2 (mm. Hg)	Mixed Venous O_2 (Vol. %)	A-V Difference (Vol. %)	O_2 Consumption (cc./min)	Cardiac Output (L./min.)	Cardiac Index (L./min./M²)	Tidal Volume (cc.)	Minute Volume (L.)	Pressures Wedge (mm./Hg)		Pulmonary Artery (mm./Hg)		Right Ventricle (mm./Hg)	Right Atrial (mm./Hg)	Brachial Artery (mm./Hg)	Pulmonary Resistance (dynes sec. cm.$^{-5}$)	
												Inspiration	Expiration	Inspiration	Expiration				Arteriolar	Total
F. L. (control subject)	18.9	15.3	80.9	39	12.1	3.2	270	8.5	4.6	410	11.9	Not obtainable		30/16 (26)	40/22	30/2–40/10	6–14	.....	...	245
Occlusion of left pulmonary artery	18.9	15.0	79.3	41	11.4	3.6	290	7.8	4.2	415	10.8	4	16	50/18 (36)	60/30	.....	.....	.....	265	370
Occlusion of right pulmonary artery (middle and lower lobes)	18.9	13.7	72.4	33	9.8	3.9	334	8.6	4.7	440	13.2	0	16	62/30 (46)	74/42	.....	.....	.....	353	428
T. B. (control subject)	16.5	14.8	89.7	61	11.2	3.6	235	6.6	3.9	525	8.4	−1	9	28/8 (20)	35/13	35/4	2.8	120/80 (100)	195	244
Occlusion of left pulmonary artery	16.5	15.1	91.5	67	11.6	3.5	232	6.6	3.9	520	8.3	−1	9	32/11 (22)	40/18	.....	.....	125/80 (100)	216	265
Occlusion of right pulmonary artery	16.5	14.5	87.6	56	10.5	4.0	217	5.4	3.2	393	9.0	5	16	48/15 (36)	59/24	.....	.....	125/80 (100)	369	530
L. S. (control subject)	26.9	23.0	86.0	50	17.2	5.8	299	5.2	2.9	877	14.0	Not obtainable		44/26 (38)	52/32	45/8	6–10	105/70 (85)	...	585
Occlusion of left pulmonary artery	26.9	21.6	80.0	33	16.2	5.4	328	6.1	3.4	907	15.4	12	23	52/35 (46)	62/42	.....	.....	110/70 (100)	380	602
Occlusion of right pulmonary artery	26.9	22.3	83.0	36	16.3	6.0	347	5.8	3.2	856	16.3	6	15	50/28 (50)	68/40	.....	.....	110/70 (95)	538	690
L. O. (control subject)	20.2	18.2	90.0	..	11.7	6.5	210	3.2	2.1	...	....	(10)		40/20 (30)		.....	.....	150/90 (120)	500	750
Occlusion of left pulmonary artery (lower lobe)	20.2	17.4	86.0	..	11.7	5.7	215	3.8	2.5	...	....	(7)		60/30 (42)		.....	.....	160/100	735	883
Occlusion of right pulmonary artery	20.2	16.7	83.0	..	11.4	5.3	210 (assumed)	4.0	2.7	...	....	(10)		70/35 (50)		.....	.....	150/90	800	1000
C. K. (control subject)	16.8	15.9	94	75	11.6	4.3	336	7.8	4.4	659	10.5	−5	8	22/6 (19)	32/14	22/0–30/8 (14)	−2 to 7	125/75 (90)	175	195
Occlusion of left pulmonary artery	16.8	16.3	97	75	11.5	4.8	369	7.7	4.3	654	11.1	−2	17	26/8 (22)	34/20	.....	.....	125/85 (95)	145	228
Occlusion of right pulmonary artery	16.8	....	....	..	....	....	...	...	...	...	....	...	..	70/35	60/22	.....	.....	90/70	...	....

NOTE: Figures in parenthesis are mean pressures.

Pulmonary resistance may be calculated from the data given both as pulmonary arteriolar and total pulmonary resistance [*11*]. The highest levels were observed in Case IV. However, in no case was there an increase in proportion to the increased flow. In Case V there was an apparent decrease in arteriolar resistance when the pulmonary artery branch to the extensively diseased lung was occluded. The resistances as calculated utilize the pressure distal to occlusion rather than the assumption of a static pulmonary capillary pressure. As pointed out, this does not always remain constant.

COMMENTS

As previously suggested, the method of temporary unilateral pulmonary artery occlusion may be a valuable tool in evaluating persons with pulmonary lesions [*2*]. Because of disease of the lung, normal ventilation-perfusion relationships may be altered so that significant venous admixture may occur [*4*]. As a result of a diminished ratio of Va/Qc, arterial blood oxygen desaturation may occur and in some cases this may be quite marked. The opposite situation in which Va/Qc is increased in the absence of a diffusion barrier tends to lower the arterial CO_2. However, this is quickly and easily compensated by a generalized decrease in alveolar ventilation. Such areas of increased Va/Qc ratio have been detected by expired air analysis [*5*] but they affect the arterial blood gases only slightly and cause no diminution in oxygen tension or saturation. Clinically, therefore, diminished Va/Qc relationships are most important and their localization and extent must be determined for a most complete evaluation of the patient with pulmonary disease.

The present study demonstrates that this parameter can be successfully evaluated by the methods described. In patients with isolated pulmonary lesions, venous admixture can be lessened or abolished by occlusion of the pulmonary artery supplying that segment and conversely if flow is increased by contralateral pulmonary artery occlusion, a further decrease in Va/Qc can be produced with resultant further decrease in systemic arterial pO_2 and hemoglobin saturation. These data may be of prime importance in determining the resectability of such a pulmonary lesion in a patient with resting arterial hypoxia. As has been shown some patients may benefit hemodynamically as well as pathologically from removal of such a lesion, namely, increase in arterial oxygen saturations and pO_2, decrease in resting minute ventilation and diminution toward normal of resting cardiac output.

Patients with diffuse bilateral pulmonary disease, especially chronic pulmonary emphysema, will show a response dependent on the degree of involvement of the two lungs. The best indices are the pressure changes in the pulmonary artery and alteration of systemic arterial oxygen saturation and oxygen tension.

The observed "pulmonary capillary" pressure changes, whether measured by directly wedging a catheter in a small branch of the pulmonary artery or distal to a cuff inflated in a main subdivision are of some interest. In certain of the cases presented it appears that this pressure may rise with occlusion. This cannot be due to changes in left atrial pressure but is most likely caused by an increase in intrathoracic pressure. Such changes have not been observed in normal persons or patients without diffuse pulmonary disease. Recent evidence indicates that wedge pressure and left atrial pressure may not always be identical [*12*]. The changes in calculated pulmonary arteriolar and total pulmonary resistances are striking. It is likely that in patients with unilateral lesions, especially in C. K. (Case V), pulmonary blood flow was shunted away toward the more normal lung [*13*]. However, in patients with bilateral disease, if equal distribution to the two lungs is assumed, it is possible to estimate the resistance of each lung separately. From this assumption, the resistance of each lung in parallel would be twice the control level. It is readily apparent however, that when circulation through one lung was obliterated by occlusion, the resistance was not doubled. The total rose only slightly and indeed, in Case V, arteriolar resistance actually fell with occlusion of the diseased lung. The unoccluded lung therefore has a fall in resistance to almost one-half of normal. The mechanism of this abrupt decline in resistance is obscure. The rapidity with which it occurs makes a humoral mechanism unlikely. Although reflex change in the pulmonary arteriolar bed is a possible explanation, the most likely mechanism seems to involve the concept of the critical closing pressure of Burton [*13,15*] and the extravascular nature of pulmonary arteriolar resistance. If the resistance to blood flow in the lung is determined, to some extent at least, by extravascular factors such as alveolar pressure

levels, any increase in flow through channels already opened could be tolerated without any significant increase in pressure. Calculated resistance thus decreases markedly in proportion to the increase in flow.

SUMMARY

1. Hemodynamic studies are reported in five patients with pulmonary disease, both localized and generalized, in whom first one main branch of the pulmonary artery and then the other was occluded.

2. With localized pulmonary lesions, occlusion of the pulmonary artery supplying that area diminished or abolished venous admixture due to a diminished local ventilation-perfusion relationship.

3. Increase in flow through pulmonary lesions by occlusion of the opposite pulmonary artery causes an increase in venous admixture and further fall in systemic arterial oxygen partial pressure and hemoglobin saturation.

4. Cardiac output, pulmonary artery pressure and respiratory minute volume changes closely paralleled changes in arterial oxygen content.

5. The method of temporary unilateral pulmonary artery occlusion has proved to be a useful adjunct in evaluation of patients with pulmonary lesions especially in determining pulmonary resectability when diffuse disease is also present.

6. Pulmonary arteriolar and total pulmonary resistances are calculated using pressure distal to an occluding balloon. These are not necessarily the same as a control wedge pressure. Only small increases in resistance were observed with respect to the increase in flow produced in the unoccluded lung and calculated resistance actually fell to approximately one-half of assumed control level.

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Intracardiac Electrocardiography in Man*

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SINCE 1945, a number of reports have appeared on intracardiac electrocardiography in man describing the technic, electrical potentials and configurations within the various cardiac chambers [*1–12*]. The present study was undertaken to define further the normal intracardiac configurations and potentials, to correlate mechanical with electrical events within the heart and to assess the practical value of the intracardiac electrocardiogram in localizing the catheter tip during cardiac catheterization.

MATERIALS AND METHODS

Catheterization of the right side of the heart was performed in 136 patients under basal conditions. Thirteen of these patients had no detectable cardiac disease and 123 were abnormal from a cardiovascular standpoint, as judged by physical examination, fluoroscopic and x-ray studies, electrocardiograms and subsequent cardiac catheterization data. The average age of the normal group was fifteen years, with a range of from five to thirty-four years. The pulmonary artery was catheterized in all thirteen normal patients.

A routine electrocardiogram was taken and consisted of standard and augmented unipolar extremity leads and precordial leads V1, V3 and V5. Intracardiac catheters of size 6F or 7F§ were used. A German silver electrode 1 mm. from the distal end of the catheter was connected by means of a wire woven into the wall of the catheter to the "V" lead of the patient cable. A five channel research recorder‖ permitted the simultaneous recording of standard lead I, the intracardiac electrocardiogram and intracardiac pressures and immediate oximetric determination of oxygen saturations. In addition, the oxygen content of blood samples was determined by Van Slyke manometric analysis.

The site of the intracardiac electrode was localized by fluoroscopy and verified by pressures and blood oxygen saturations. By withdrawing the catheter slowly from the pulmonary artery to the right ventricle, it was possible by continuous pressure recording to determine the positions of the main pulmonary artery and the outflow tract of the right ventricle and, in like manner, by withdrawing slowly across the tricuspid valve to identify the inflow tract of the right ventricle and the lower part of the right atrium, and to record the intracardiac electrocardiogram from these sites. Coronary sinus positions were identified by fluoroscopic appearance and by markedly reduced oxygen saturation of the blood. Localization in the superior vena cava, mid- and high right atrium and mid-right ventricle was provided primarily by fluoroscopy, although pressure recordings and blood samples also were taken.

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‖ Electronics for Medicine, White Plains, New York.

RESULTS

The Normal Intracardiac Electrocardiogram. An analysis of the intracardiac electrocardiogram in the thirteen normal subjects is presented in Tables I, II and III. As shown in Table I, the total voltage of the P wave in the pulmonary artery and right ventricle varied considerably but was usually less than 0.5 mv. In the right atrium the voltage was higher, varying from 0.5 to 1.5 mv. The P wave was positive in the lower portion, diphasic in the mid-part and inverted in the upper part of the right atrium. (Fig. 1A.) No such consistency in P wave polarity was seen in the right ventricle and pulmonary artery. P waves recorded from the pulmonary artery or right ventricle were either slightly positive or negative, or isoelectric.

Normal potential variations of the QRS complex are presented in Table II. Outside the right ventricle the total QRS deflection was on the average 2 to 3 mv. in amplitude and within the right ventricle 9 to 13 mv. Considerable variation was encountered in the latter. The total QRS voltage ranged from 5.0 mv. (still much higher than the QRS of the superior vena cava, right atrium or pulmonary artery) to 18.3 mv. All but one patient had a small (1 to 2 mv.) r wave at some site in the right ventricle, but the

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TABLE I
ANALYSIS OF P WAVES (MV.) IN THIRTEEN NORMAL SUBJECTS

Location	Positive			Negative			Isoelectric (no.)
	Mean	Range	No.	Mean	Range	No.	
Main pulmonary artery	0.2	0.2	1	0.3	0.1–0.5	7	5
Outflow tract of right ventricle	0.5	0.3–0.9	3	0.3	0.3	2	4
Mid-right ventricle	0.3	0.2–0.4	7	...	.....	...	3
Inflow tract of right ventricle	0.5	0.2–1.2	7	...	.....	...	3
Low right atrium	0.5	0.2–1.3	10	...	.....	...	2
Mid-right atrium	...	.....	..	0.5	0.3–0.9	3*	8†
High right atrium	...	.....	..	1.5	0.7–3.2	12	...
Superior vena cava	...	.....	..	0.5	0.2–2.0	10	1

* Diphasic but predominantly negative.
† Diphasic with equal positive and negative deflections.

predominant deflection always was negative. The characteristic QRS pattern in the right ventricle was a large QRS complex (9 to 13 mv.) containing a small r wave and a deep S wave.

In contrast to that observed within the right ventricle the QRS deflection outside the right ventricle was much smaller (2 to 3 mv.) but predominantly negative. Usually there was a deep Q wave in the upper and mid-right atrium, and a small r and deep S wave in the main pulmonary artery. However, in five patients the main pulmonary artery pattern showed a deep Q wave, followed by a small r wave in two of the five. The rSr′ pattern in the main pulmonary artery was encountered in but two of thirteen patients. The QRS voltage range outside the ventricle was similar at all sites. The average voltage in the main pulmonary artery was 2.6 mv., whereas in the right atrium it ranged from 2.4 to 3.1 mv., the latter being in the low portion

TABLE II
ANALYSIS OF TOTAL QRS VOLTAGE (MV.) IN THIRTEEN NORMAL SUBJECTS

Location	Mean	Range
Main pulmonary artery	2.6	1.6– 3.8
Outflow tract of right ventricle	9.7	7.7–15.6
Mid-right ventricle	12.7	7.0–18.3
Inflow tract of right ventricle	9.7	5.0–17.8
Low right atrium	3.1	1.0– 4.9
Mid-right atrium	2.3	1.6– 3.7
High right atrium	2.4	1.3– 3.3
Superior vena cava	1.9	0.8– 2.6

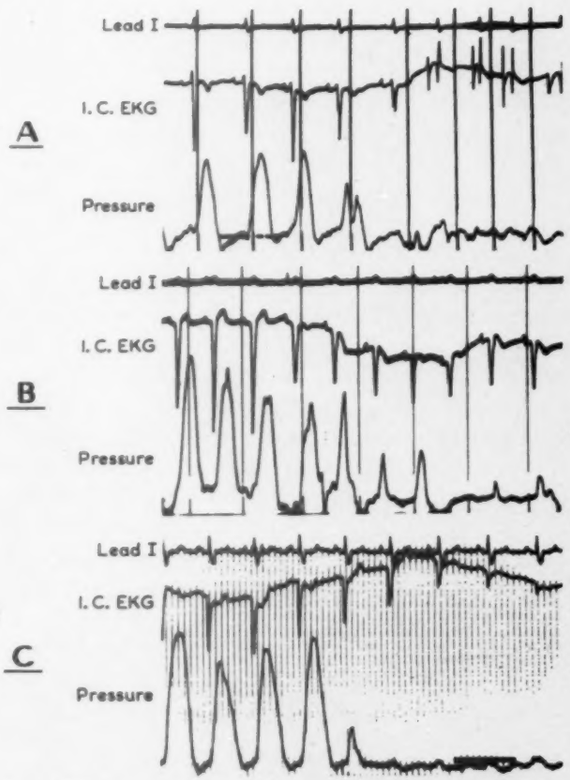

FIG. 1. Electrocardiographic-pressure relationship. Three pullbacks across the tricuspid valve from RV to RA. A, simultaneous change in pressure and electrocardiogram. In the last 5 beats the intracardiac electrocardiographic pattern changed from a low right atrial pattern (positive P wave) to mid-atrial electrocardiogram with a larger atrial deflection that is diphasic to, on the last beat, a high RA electrocardiographic pattern (negative P wave). B, electrocardiographic changes to a low RA pattern before a corresponding change in pressure. C, the change from a RV pressure to an RA pressure precedes the appearance of the atrial electrocardiogram.

FIG. 2. Tracings from the coronary sinus. The salient feature of a commonly observed coronary sinus pattern is a tall notched R wave.

of the right atrium in close proximity to the right ventricle. While not identical, the configuration of the QRS was similar in the pulmonary artery and right atrium in that the deflections were predominately negative. At times this was due to a qr deflection and, at other times, to an rs deflection.

Table III shows the uniformity of the T wave pattern in the intracardiac tracing in the normal group of thirteen patients. The T wave was negative at all but one of the recorded sites. The single diphasic T wave was considered to be due to an injury current. The average voltage of the T wave was similar at all sites, usually from 0.5 to 2 mv., although slightly higher voltages were found in the right ventricle than in either the pulmonary artery or the right atrium, and in the superior vena cava the voltage was somewhat less (0.5 mv.). There was no relationship between the magnitude of the voltages of the QRS complexes and T waves. The ratios of QRS/T varied from 14/3 to 2/1.

Since the coronary sinus was catheterized in but two of the thirteen normal patients, no normal standards can be tabulated for this site.

TABLE III
ANALYSIS OF T WAVES (MV.) IN THIRTEEN NORMAL SUBJECTS

Location	Mean	Range
Main pulmonary artery	−0.9	−0.3 to −2.2
Outflow tract of right ventricle	−1.7	−0.4 to −3.0
Mid-right ventricle	−2.1*	−0.8 to −4.0
Inflow tract of right ventricle	−2.1	−0.7 to −3.7
Low right atrium	−0.9	−0.3 to −1.4
Mid-right atrium	−1.0	−0.6 to −2.0
High right atrium	−0.7	−0.3 to −1.0
Superior vena cava	−0.5	−0.2 to −1.0

* One T wave diphasic, probably current of injury.

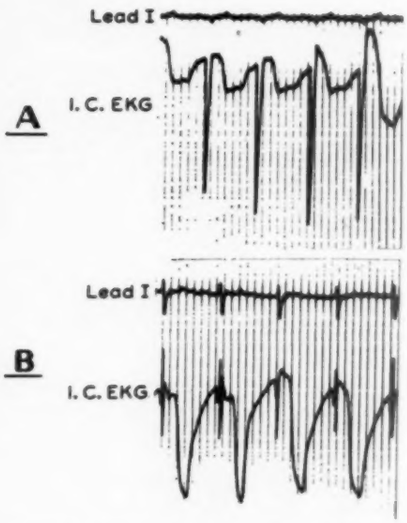

FIG. 3. Current of injury. A, progressive ST displacement in the right ventricular electrocardiogram. B, marked T wave inversion with accompanying distortion of the QRS complex due to impingement of the catheter against the endocardium.

However, a commonly observed coronary sinus pattern in fourteen of the total group of 136 is that depicted in Figure 2. The distinctive feature was a tall R wave, although considerable variation in pattern was encountered.

UNUSUAL FEATURES OF THE INTRACARDIAC ELECTROCARDIOGRAM

A number of unusual features were observed on intracardiac recordings which were not found on the surface electrocardiogram. These have been selected from the total series of thirteen "normal" and 123 "abnormal" records and include (1) injury pattern, (2) respiratory variations, (3) pressure and electrocardiographic discrepancies, (4) variable conduction on simultaneous leads, and (5) intracardiac electrical and pulsus alternans.

Injury Pattern. A characteristic current of injury appeared when the catheter impinged upon the endocardial surface. Progressive displacements of the ST segment are illustrated in Figure 3. This injury current was not manifest on simultaneously recorded lead I and was transient. Its appearance often was followed by diphasic and, then, deeply inverted T waves as the ST segment became isoelectric. Similar displacements of the PQ (or PR) segment resulted from catheter pressure against the endocardium of the right atrium. (Fig. 4.) Impingement of the catheter against the endocardial wall

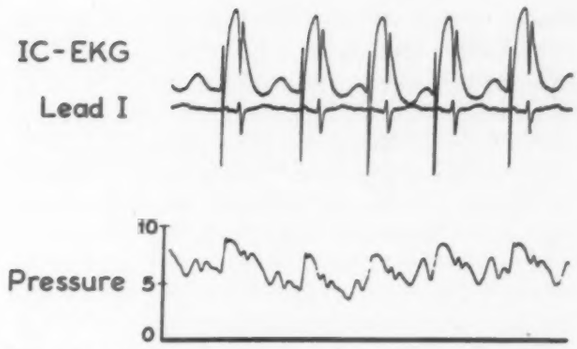

FIG. 4. Atrial injury. Illustrates PQ segment displacement, following a large diphasic mid-right atrial P wave.

of the right ventricle often, but not always, caused damping of the pressure wave (Fig. 5) and was associated with difficulty in withdrawing blood samples.

Respiratory Variations. As shown in Figure 6, some variation in voltage commonly was encountered associated with the respiratory cycle. The magnitude of this variation was small, usually less than 0.5 mv. outside the ventricle and up to 2.0 mv. in the right ventricle. From a qualitative standpoint, the respiratory variation occasionally caused the loss or gain of a positive deflection.

Pressure–Electrocardiographic Discrepancy. In general, the cardiac chambers and accessible

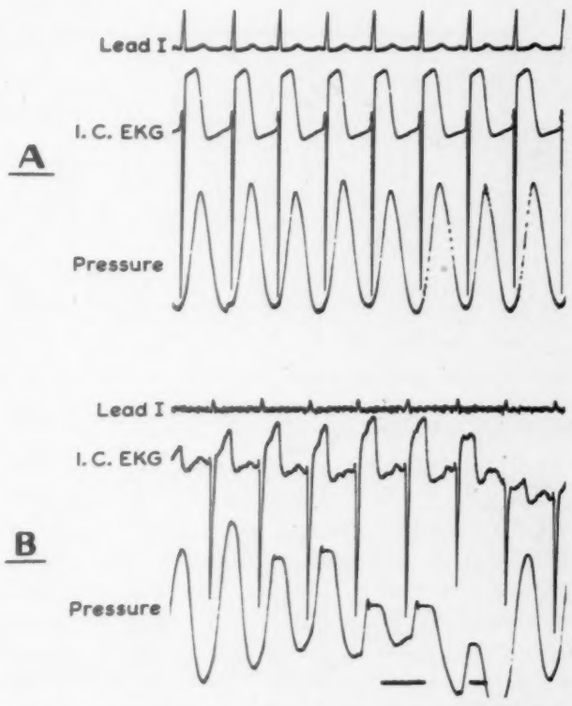

FIG. 5. Pressure recording in the presence of an injury current. A, right ventricular injury current not associated with significant pressure damping. B, progressive ST elevation (injury current) with concomitant pressure damping. Such pressure artifacts accompanying injury currents are common when the catheter impinges against the ventricular endocardium.

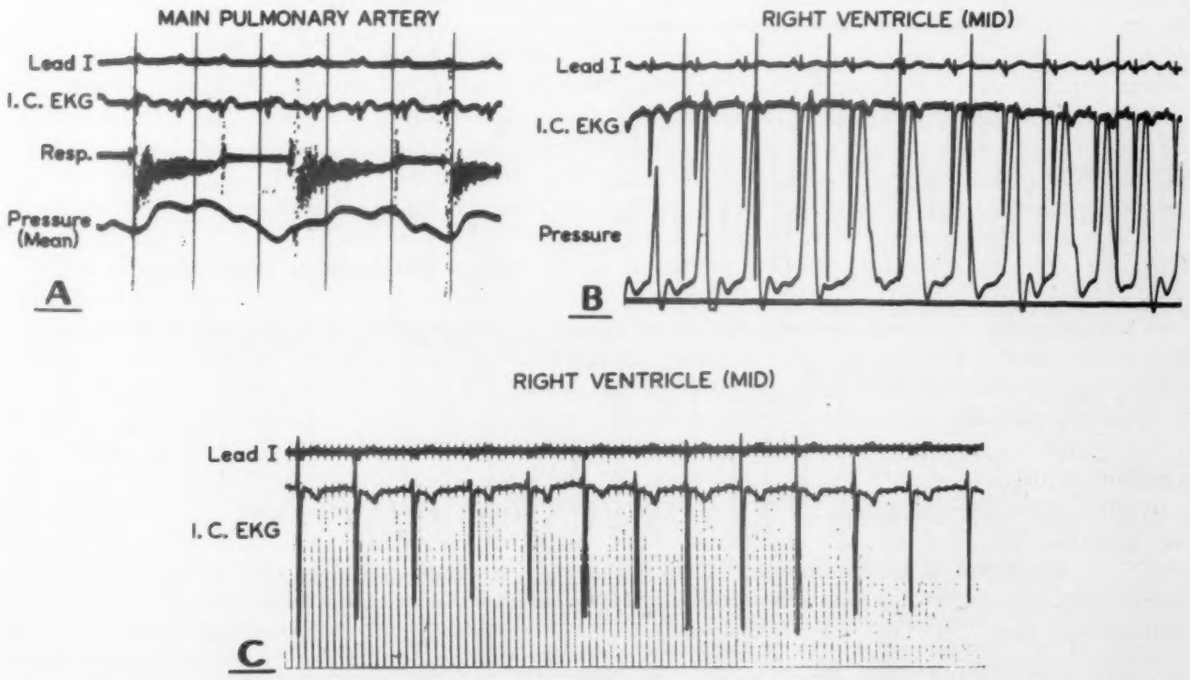

FIG. 6. Respiratory variation. Changes in configuration of the QRS complex associated with the respiratory cycle.

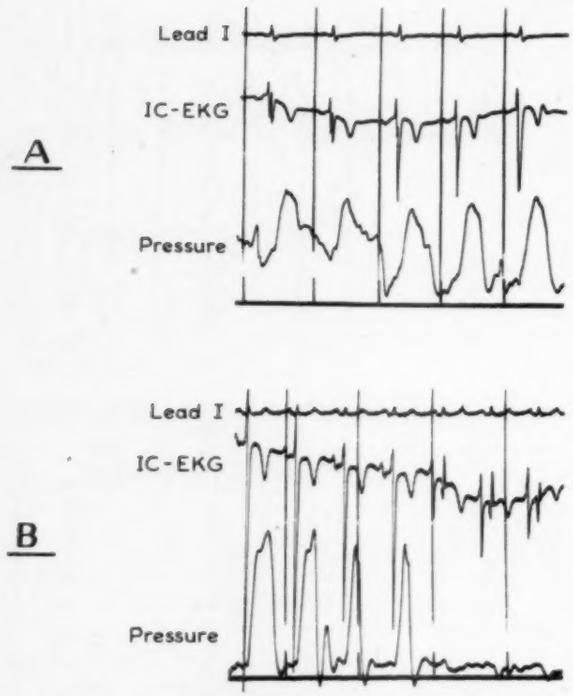

FIG. 7. Normal "pullback." A, simultaneous change in intracardiac electrocardiogram and pressure is seen on withdrawing the catheter across the pulmonic valve to the right ventricle. B, similarly, simultaneous change in pressure and intracardiac electrocardiogram is noted on crossing the tricuspid valve to the right atrium.

vessels could be identified as well from the intracardiac electrocardiogram as by recording pressures. However, in some patients, a small pressure-electrocardiographic discrepancy was noted at both the pulmonic and tricuspid valves. An example of the usual "pullback" is presented in Figure 7. As the catheter was withdrawn across the pulmonic valve from the pulmonary artery to the right ventricle, the pulmonary artery pressure changed to a right ventricular pressure and the small voltage pulmonary artery electrocardiogram assumed the form of the larger voltage right ventricular electrocardiogram. Similarly, as the catheter passed from the right ventricle to the right atrium across the tricuspid valve, a simultaneous change in pressure and electrocardiogram from ventricular to atrial patterns occurred. Excluding two patients with pressure gradients across the pulmonic valve, on sixty-three occasions in which pullbacks from the pulmonary artery to the right ventricle were analyzed, it was found that pressure change preceded the electrocardiographic change eight times, and on one occasion the electrocardiographic change to a right ventricular pattern preceded the appearance of a right ventricular pressure. In twenty-nine instances the pressure and intracardiac electrocardiogram

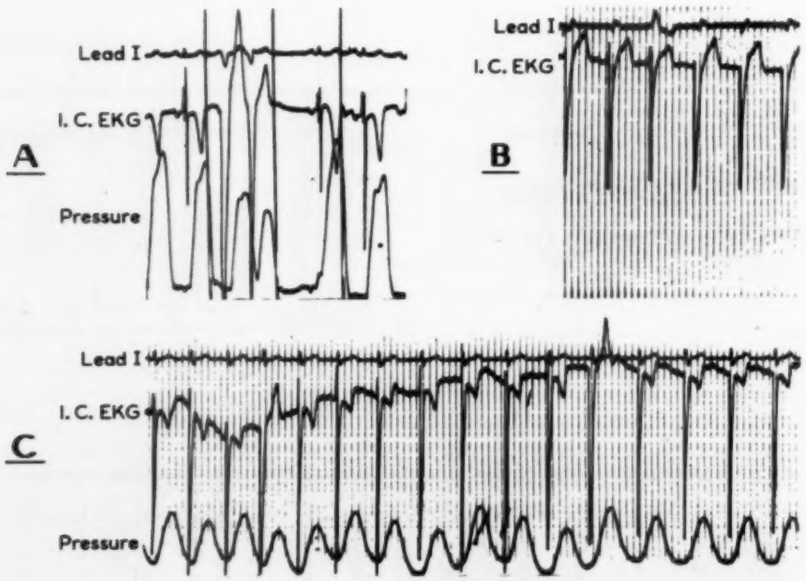

FIG. 8. Extrasystoles and aberrant conduction. A, ventricular extrasystoles appearing on simultaneously recorded standard lead I and the intracardiac right ventricular electrocardiogram. B, aberrant conduction obvious in lead I and not readily apparent in the intracardiac electrocardiogram. C, aberrant conduction (beats 4 and 12) present in the right ventricular electrocardiogram and not discernible on standard lead I.

changed to a right ventricular pattern simultaneously, and in twenty-five instances ventricular premature contractions obscured the transitions. Similarly, during ninety-seven pullbacks from right ventricle to right atrium across normal tricuspid valves, pressure change preceded electrocardiographic change seventeen times (Fig. 1C), electrocardiographic change preceded pressure change twelve times (Fig. 1B), the transitions were simultaneous on sixty-six occasions, and were obscured by ventricular premature contractions on two pullbacks. Pressure preceded electrocardiographic change or vice versa by no more than 3 beats on any of the records examined, although the usual discrepancy was 1 to 2 beats. This pressure-electrocardiographic discrepancy was not due to the relative locations of the pressure and electrocardiographic recording devices on the catheter since the electrode was but 1 mm. proximal to the catheter tip and either pressure or electrocardiographic change occurred first.

Variable Conduction on Simultaneous Leads. The frequent occurrence of extrasystoles as the catheter passed through the right ventricle provided an opportunity to study the detection of extrasystoles on simultaneously recorded lead I and the intracardiac electrocardiogram. In general, ventricular extrasystoles were readily apparent on either lead and were easily distinguishable from normal systoles. Ventricular extrasystoles seen on the intracardiac electrocardiogram were premature beats which were occasionally interpolated, with a QRS duration of 0.12 seconds or greater, increased voltage and T waves generally opposite the main deflection of the QRS. Infrequently, aberrant conduction was apparent on one lead and not on the other. (Fig. 8.)

Intracardiac Electrical and Pulsus Alternans. In two infants with septal defects, intracardiac electrical and pulsus alternans were noted simultaneously. Figure 9 is a catheterization record from a five month old infant who had congestive heart failure and a large ventricular septal defect at autopsy. In this tracing there is a 40 per cent decrease in QRS voltage (equal to 9.0 mv.) in the right ventricle between the large and small beats of the alternans couple, whereas the voltage change in lead I is but 0.05 mv., a change that easily might be overlooked. In the second case, an infant with congestive heart failure and a large atrial septal defect proved at postmortem, pulsus alternans was accompanied by electrical

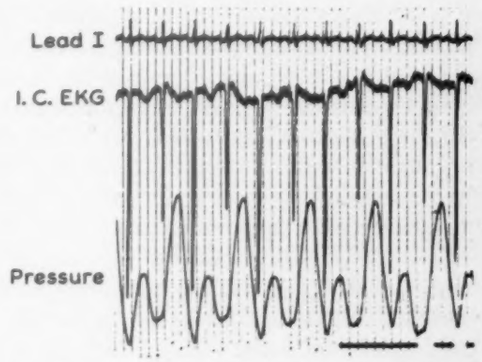

FIG. 9. Pulsus alternans. Simultaneous electrical and mechanical alternans are present on intracardiac recordings but electrical alternans is barely discernible on standard lead I.

alternans too small to be seen on the limb leads but easily demonstrable on the intracardiac electrocardiogram. It is of interest that the large voltage QRS complex of the alternans couple precedes the small pressure beat, just as the large voltage of extrasystoles precedes a small pressure beat. However, the large voltage complex and small beat of the alternans couple are not premature. The explanation for this phenomenon is not apparent.

COMMENT

The intracardiac electrocardiogram is sufficiently characteristic in the various chambers and vessels to permit accurate localization of the catheter tip during cardiac catheterization. The superior vena cava and atrial electrocardiograms consist of relatively large P waves, generally inverted in the superior vena cava and high in the right atrium, diphasic in mid-atrium and positive in the lower portion of the atrium. In contrast to the relatively large P waves, the mean total QRS voltage within the superior vena cava or right atrium is relatively small. The ventricular electrocardiogram demonstrates isoelectric or relatively small P waves while the QRS complex is unmistakably large. The electrocardiogram recorded from the pulmonary artery resembles the atrial electrocardiogram in that the mean QRS voltage is small, but differs in that the P waves are of similar magnitude to those observed within the ventricle and of much less amplitude than in the right atrium.

Although the configuration of the atrial electrocardiogram described was essentially that described by Levine, Kossmann and coworkers [*6,11*], the mean P wave voltage was

found to be somewhat greater at all levels within the atrium. The total QRS voltage within the heart chambers was also found to be greater than that observed by Kossmann in fourteen patients with normal hearts [*11*]. The absence of an initial r wave at some site in the right ventricle was noted by Levine in three of twenty-seven patients and by Kossmann in two of fourteen patients [*7,11*]. Similarly, in one of our thirteen patients, an initial r wave was not discernible at some site within the ventricle.

Variations in both the voltage and configuration of the intracardiac complexes were encountered but were not of sufficient magnitude to preclude recognition of characteristic patterns. Variations of voltage within a chamber may actually be an aid to accurate localization of the catheter tip. For example, the mean QRS voltage was greater in the mid-ventricle than in the outflow or inflow tracts.

Respiratory variations of voltage have been noted by others [*5*] and are described herein. These were of small magnitude, and did not detract from the localizing value of the intracavitary lead. QRS voltage within the ventricle or the height of r or r′ in the pulmonary artery varied with respiration. Possibly movement of the heart and/or changes in stroke volume or pressure with respiration may alter the relationship of the intracardiac electrode to the electrical field of the heart, either by displacement of the catheter tip or by alteration in the flow of conducting medium between the myocardium and the electrode.

An electrocardiographic and pressure discrepancy of 1 to 3 beats occurred as the catheter was withdrawn across the pulmonic or tricuspid valves in almost one-third of the pullbacks, but this discrepancy did not interfere with identification of the catheter site by intracardiac electrocardiogram. Although of short duration, such variability across normal pulmonic valves indicates that caution must be used in utilizing the intracardiac electrocardiogram to distinguish infundibular from valvular stenosis [*13*].

Thus, despite the minor variations in voltage and configuration described, the intracardiac electrocardiogram provides a useful technical aid in localizing the catheter tip during the catheterization procedure. Its usefulness extends in two other directions: (1) obtaining accurate pressure measurements at the time of catheterization and (2) the detection of phenomena within the heart which are not apparent on surface electrocardiograms.

The injury pattern, particularly its effects on the ST and T wave in the ventricle and the PQ segment in the atrium, has been described by Hellerstein and Katz [*14*], Pruitt, Barnes and Essex [*15*] in dogs, and by Levine [*7*] and Prinzmetal and co-workers [*16*] in man and has usually been attributed to contact of the catheter tip with the endocardium. It has been demonstrated that the superficial layers of the myocardium exert a much greater influence on the surface electrocardiogram than do the endocardial or subendocardial layers [*15–17*], and it is to be expected that the injury pattern might be demonstrable on the intracavitary lead while absent in a simultaneously recorded surface lead. Contact of the catheter tip with the endocardium may cause damping of the pressure tracing which, by means of the injury pattern on the intracardiac electrocardiogram, may be recognized as artifact. For example, in a patient with a high right ventricular pressure, a damped pressure curve obtained from the right ventricular outflow tract might be interpreted as a pulmonary artery curve and an erroneous diagnosis of pulmonic stenosis might be made. The recognition of the injury current obviates such an error. An excellent discussion of the interpretation of catheterization findings, and possible erroneous conclusions resulting from damped pressure curves has been presented by Fowler [*18*].

The injury pattern is but one of several phenomena detectable within the heart but not readily apparent on surface leads. Aberrant conduction not obvious on surface leads may be seen, and supraventricular arrhythmias such as flutter, fibrillation or tachycardia are readily differentiated by the intracardiac electrode when uncertainty may exist about the diagnosis from a surface electrocardiogram. Electrical alternans, not apparent on routine electrocardiography, may be detected easily on the intracavitary electrocardiogram, probably because of the greater voltages recorded within the heart as compared to the more remote surface leads. In the right ventricle, the voltage is approximately tenfold higher than on the routine standard lead. Electrical alternans is seen frequently in the absence of pulsus alternans, and often in the absence of any demonstrable heart disease. Pulsus alternans, while often seen in cardiac disease of significant nature, may be unaccom-

panied by simultaneous electrical alternans. Possibly, the infrequently reported simultaneous occurrence of electrical and mechanical alternans is related to the difficulty in detection of small voltage changes on surface leads, and it is conceivable that many instances of mechanical alternans are actually accompanied by electrical alternans undetected by routine electrocardiography.

An important indication for more widespread use of the intracavitary electrocardiogram as a routine adjunct to the catheterization procedure is its value as a protective measure for the patient. Both endocardial trauma and unrecognized coronary sinus catheterization are reported dangers of cardiac catheterization [*19*]. The transient injury pattern warns of contact with the endocardium, and the appearance of the coronary sinus pattern avoids unrecognized catheterization of the coronary sinus. The rapid identification of arrhythmias with the intracavitary lead enables prompt, specific therapy to be instituted if the arrhythmia does not abate upon withdrawal of the catheter. In addition, the amount of screening time is decreased when the intracardiac electrode is used. Since it is usually possible to guide the catheter into the right atrium and right ventricle, avoiding passage of the catheter into the jugular vein by palpation of the neck, by means of the intracardiac electrocardiogram, radiation exposure to patient and operator is decreased.

SUMMARY AND CONCLUSIONS

1. During routine cardiac catheterization in thirteen normal patients and 123 patients with cardiovascular abnormalities, the intracardiac electrocardiogram was recorded with simultaneous intracardiac pressures and standard lead I. The normal configuration and potentials are described for the various chambers and accessible vessels.

2. The configuration and potentials of the normal intracardiac electrocardiogram are sufficiently characteristic to permit accurate localization of the catheter tip. The occurrence of respiratory variations or of an electrocardiographic-pressure discrepancy has been noted, but this is of insufficient magnitude to preclude chamber localization.

3. An injury pattern appears when the catheter tip impinges on the ventricular endocardium (ST elevation, deeply inverted T waves) or the atrial endocardium (PQ elevation), whereupon the catheter may be withdrawn slightly in order to obtain accurate pressure recordings and blood samples.

4. Intracardiac electrocardiography facilitates the detection of phenomena within the heart which are not readily apparent on surface leads. In addition to the injury pattern, these include aberrant conduction and electrical alternans. Two infants with severe congenital heart disease are discussed with regard to the simultaneous occurrence of electrical and mechanical alternans. While the degree of voltage change in the right ventricle was great enough to make electrical alternans readily apparent, the voltage change on a simultaneously recorded surface lead was so small as to be overlooked easily.

5. Intracardiac electrocardiography is a protective measure for the patient because it warns of impending endocardial trauma and unrecognized coronary sinus catheterization, permits rapid identification of the type of arrhythmia and decreases radiation exposure.

6. It is suggested that this technic be used as a routine adjunct to cardiac catheterization.

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Incidence and Significance of Abnormal Hemoglobins*

Report of a Series of 1,000 Hospitalized Negro Veterans

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PAPER electrophoresis provides an easy, reliable and economical method for the detection of major and minor hemoglobin abnormalities. This technic is well suited to the screening of large groups of patients for clinical and genetic purposes. This is a study of the incidence and possible clinical significance of abnormal hemoglobins in a series of 1,000 consecutive Negro patients admitted to the Veterans Administration Hospital, Philadelphia, Pennsylvania.

MATERIALS AND METHODS

Hemoglobin determinations were performed on the first 1,000 Negroes admitted to all services of the hospital between January 23, 1957 and February 6, 1958. Patients readmitted during this period were counted only as a single admission. There was an age range from twenty-two to ninety-two years. There were only three females in the group, a reflection of the overwhelmingly male population of this hospital.

Hemoglobin solution was prepared from heparinized venous blood. Five to 10 ml. of blood were centrifuged at 2,000 r.p.m. for ten minutes and the plasma aspirated and discarded. Ten ml. of physiological saline solution were added to the packed red cells and stirred gently to insure thorough mixing. The mixture was then centrifuged for ten minutes following which the supernatant was withdrawn, discarded, and the cells washed three more times in a similar manner. Two volumes of barbital buffer (pH 8.6) were added for each volume of packed red cells. The mixture was then stirred gently and placed in a freezing compartment. Barbital buffer (pH 8.6 with ionic strength 0.050) was prepared from 1.84 gm. diethylbarbituric acid and 10.30 gm. sodium diethylbarbiturate per liter of distilled water.

Prior to use, the hemoglobins were thawed at refrigerator temperature of 4°C. and centrifuged for ten minutes to separate the clear hemolysate from cell debris. A Spinco model R paper electrophoresis system containing barbital buffer was used. 0.01 ml. of hemoglobin solution was applied to each paper strip and the hemoglobins were separated at 7.5 milliamperes per cell constant current for sixteen hours. The separation was carried out at refrigerator temperature of 4°C. A normal A control was placed on the first paper strip and a CS control on the eighth strip. Six unknowns were determined in each run. Percentages of abnormal hemoglobins were estimated by the Spinco model R Analytrol.

Alkali denaturation tests for fetal hemoglobin were performed on all hemoglobin samples by the method of Singer et al. [*1*]. Hemoglobin S, which has a low ferro-hemoglobin solubility, was distinguished from hemoglobin D, which has a high solubility, by Goldberg's modification of Itano's method [*2,3*].

RESULTS

The results of the hemoglobin determinations are shown in Table 1 and compared with four other large groups similarly studied in different hospitals [*4–7*]. The percentages of abnormalities are similar in each series despite the fact that there were some differences in the groups of patients studied. In our series, for example, only adults were tested and it might be expected that fewer major hemoglobinopathies would be encountered. There were, however, three cases of SS disease and two of SC disease in the group. In addition, there were seventy-four patients with sickle trait (AS hemoglobin), twenty-three patients with C trait (AC hemoglobin), and four patients with miscellaneous abnormalities including one with D trait and three with excessive amounts of F hemoglobin.

The records of all patients with hemoglobinopathies were reviewed in an attempt to correlate, if possible, the clinical pictures with the abnormal hemoglobins.

As already mentioned, seventy-four patients

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TABLE I

INCIDENCE OF ABNORMAL HEMOGLOBINS IN SEVERAL LARGE GROUPS OF NEGROES

Series	No. of Patients	AS Sickle Trait	SS Sickle Disease	S-C	AC C Trait	CC	Others
Smith and Conley [4]	500	36 (7.2%)	5 (1.0%)	1 (0.2%)	9 (1.8%)	0	0
Schneider [5]	1,550	139 (9.0%)	4 (0.3%)	1 (<0.1%)	35 (2.3%)	0	2* (0.1%)
Haynie, Dobson and Hettig [6]	400	36 (9.0%)	5 (1.3%)	1 (0.25%)	6 (1.5%)	1 (0.25%)	0
Chernoff [7]	1,000	94 (9.4%)	0	0	26 (2.6%)	0	4† (0.4%)
Myerson, Harrison and Lohmuller	1,000	74 (7.4%)	3 (0.3%)	2 (0.2%)	23 (2.3%)	0	4‡ (0.4%)
Total	4,450	379 (8.5%)	17 (0.4%)	5 (0.1%)	99 (2.2%)	1 (<0.1%)	10 (0.2%)

* Two patients with thalassemia and increased F hemoglobin.
† Four patients with AD hemoglobin.
‡ One patient with AD hemoglobin and three with increased hemoglobin F.

with AS hemoglobin were detected (7.4 per cent of the total group). The amount of A hemoglobin averaged 57 per cent, with extremes of 43.5 per cent and 78 per cent. Perusal of the clinical records of patients with AS hemoglobin revealed the presence of gross hematuria in three patients. In one of these a left nephrectomy had been performed in 1950 because of the finding of an abnormal left kidney on intravenous and retrograde urography. Examination of the histological sections in this patient revealed evidences of renal infarcts. Anemia was present in some patients in this group, but there was always an adequate explanation for its presence. Although sickling occurred in the red blood cells of all AS patients *in vitro*, there was no definite evidence that *in vivo* sickling took place.

Twenty-three patients manifested C trait or an AC hemoglobin pattern. The percentage of A hemoglobin in these patients varied from 51 per cent to 70 per cent with a mean of 59 per cent. Perusal of the clinical records of these patients revealed one patient with repeated episodes of gross hematuria for which no responsible genitourinary abnormality could be discovered. Several patients with C trait were noted to have few to moderate numbers of target cells in the blood smear. In neither these patients nor the patients with sickle cell trait were any roentgenographic abnormalities of the bones noted. One patient with AC hemoglobin died of acute vertebral osteomyelitis due to Aerobacter aerogenes associated with septicemia and diabetes. Although the association of osteomyelitis with the major hemoglobinopathies such as SS and SC disease has been well recognized, the assumption of such an association does not seem to be warranted in this particular case.

Of three patients with pure S disease, two had known sickle cell disease and were admitted to the hospital during the period of survey with symptoms referable to acute sickle cell crises. The third patient in this group was a fifty-seven year old Negro with a post-traumatic paraplegia, pulmonary emphysema and pneumonia. The patient's hemoglobin varied between 8 and 10 gm. per cent. There was isosthenuria with a specific gravity of 1.010. Blood smears were positive for sickling and the hemoglobin electrophoretic pattern revealed a pure S plus 5.5 per cent hemoglobin F.

Two patients with CS hemoglobin were detected in the survey. The first was a twenty-six year old man admitted for a hydroceletomy. Except for his hydrocele, physical examination was within normal limits. His hemoglobin was 13.5 gm. per cent and hematocrit 44 per cent. A moderate number of target cells were noted in the peripheral smear and the sickle cell test was positive. His urine concentrated to 1.014. There were 5 to 10 red blood cells per high power field in the urinary sediment. The patient had 57 per cent C hemoglobin, 43 per cent S hemoglobin. The second patient with CS disease was a thirty year old Negro with a history of recurrent hematuria. A left nephrectomy had been performed at another hospital in 1953 following an episode of hematuria. Retrograde and intravenous urograms at that time had revealed a filling defect in the left renal pelvis. Histologic examination of the kidney revealed multiple renal infarctions. Splenomegaly was present and

there was an anemia of 10 gm. per cent. An *in vitro* sickle cell test was positive. This patient had 56.5 per cent C hemoglobin, 43.5 per cent S hemoglobin.

There was a miscellaneous group of four patients. One of these was a thirty-three year old woman who had been admitted because of thrombophlebitis. Routine hemoglobin electrophoresis revealed an AD pattern with 43 per cent A hemoglobin, 57 per cent D hemoglobin. There were no clinical or laboratory abnormalities. Three patients had excessive quantities of F hemoglobin associated with a normal A pattern. One of these was a thirty-six year old man with a diagnosis of chronic alcoholism and antisocial personality. Hemoglobin analysis revealed 2.6 per cent hemoglobin F. Further studies revealed a hemoglobin of 12.3 gm. per cent and a hematocrit of 39. A few target cells were noted in the peripheral smear. The reticulocyte count was 3.2 per cent. Results of the Coombs' test were negative. The patient had increased resistance to hemolysis by hypotonic saline solution and the diagnosis of thalassemia minor was made. The second patient was a fifty-nine year old Negro admitted to the hospital with an acute hemolytic anemia of undetermined etiology. At the time of admission, physical examination was within normal limits. He had a hemoglobin of 6 gm. per cent of which 2.7 per cent was hemoglobin F and the remainder A. The patient responded to therapy with streoids, and following subsidence of the acute hemolytic episode no hemoglobin F could be demonstrated. The third patient was a thirty year old Negro with a history of recurrent icterus, diagnosed on one occasion as hepatitis. Subsequently he was found to have cholelithiasis and a cholecystectomy was performed. He was admitted complaining of recurrent severe colicky pain in the right upper quadrant. Physical examination revealed a slightly enlarged liver but was otherwise within normal limits. Laboratory studies including hemoglobin, hematocrit and liver function tests, roentgenograms of the upper and lower gastrointestinal tract, skull and long bones were negative. Two intravenous cholangiograms were negative for residual biliary tract calculi. Repeated hemoglobin analyses revealed the persistence of 20 to 30 per cent fetal hemoglobin. The reticulocyte count was 0.4 per cent. Coombs' tests were negative. Red blood fragility tests were within normal limits and a sickle cell preparation was negative. All attempts to explain this patient's elevated hemoglobin F were unsuccessful.

COMMENTS

The 10.6 per cent incidence of hemoglobin abnormalities noted in this survey corresponds closely to that reported in the other series [*4–7*] (Table 1) and emphasizes the potential clinical significance of these disorders. In some areas in which the incidence of diseases secondary to infection, parasites and malnutrition has been markedly reduced, the hemoglobinopathies have assumed serious proportions [*8*].

Despite the apparent importance of major abnormalities such as SS and SC disease, it is evident that their course may be relatively benign. As reported, one fifty-seven year old patient had unsuspected sickle cell disease unaccompanied by any of the usual stigmas and the only abnormality was a hemoglobin of 10 gm. per cent. One of the two patients with SC disease had no signs or symptoms referable to the disorder.

The potential importance of the sickle cell trait has been emphasized by a number of recent reports concerning splenic infarction in these patients, during and after airplane flights [*9–16*]. Hematuria occurs in sickle cell trait [*17*] and in one patient in this series a nephrectomy had been performed because of it. One patient with C trait also manifested hematuria. Thoma mentions that sickle cell trait may be responsible for unexplained sudden deaths [*18*]. It is apparent, therefore, that the supposed clinical benignity of the trait hemoglobinopathies must be questioned. The mechanisms involved in the production of these phenomena in patients with sickle cell trait are as yet unsettled. There is evidence that prolonged exposure of blood to low oxygen tensions and reduced pH may be responsible for splenic and possibly renal infarctions [*19–25*].

SUMMARY AND CONCLUSIONS

Hemoglobin electrophoresis was performed in blood samples of 1,000 consecutive hospitalized Negro veterans. Abnormalities were detected in 10.6 per cent, a figure comparable to that of other large series.

The abnormalities included seventy-four patients with AS hemoglobin, twenty-three with AC, three with SS, two with SC and one with AD. Three patients had increased amounts of F hemoglobin.

A survey of the clinical records of these patients revealed three instances of gross hematuria

in the AS group, one in the AC group and one in the SC group. Nephrectomy had been performed in two of these five patients. One patient with SC disease was asymptomatic and the only abnormality in a fifty-seven year old man with SS hemoglobin was a moderate anemia.

This study re-emphasizes the potential clinical and genetic importance of the hemoglobinopathies and questions the supposed benignancy of the trait patterns.

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The Role of Splenectomy in the Management of Acquired Autoimmune Hemolytic Anemia Complicating Systemic Lupus Erythematosus*

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ACQUIRED autoimmune hemolytic anemia has been detected in 3 to 10 per cent of the cases of systemic lupus erythematosus [*1–3*]. Appropriate investigations of patients with systemic lupus erythematosus would probably reveal a higher incidence, for a positive direct Coombs' test, indicating sensitization of erythrocytes, has been demonstrated in 25 per cent of patients with systemic lupus erythematosus [*1–3*]. Often the management of these cases is identical with that commonly used in uncomplicated cases of systemic lupus erythematosus since steroid therapy may be effective in producing palliation of both systemic lupus erythematosus and acquired autoimmune hemolytic anemia. Under the influence of steroid therapy the clinical manifestations of systemic lupus erythematosus are more greatly benefited than is the hemolytic state [*1*]. Most patients respond well enough to assure an adequately compensated hemolytic state, but remission of the hemolytic state does not occur in all instances. This group of patients requires the application of other therapeutic methods. Reported experiences with this therapeutic problem are not in general agreement. Recently it has been stated that splenectomy is contraindicated in patients with systemic lupus erythematosus [*4*]; however, our experience leads us to believe that splenectomy can be quite helpful and even life-saving.

We have studied three patients with systemic lupus erythematosus, complicated by autoimmune acquired hemolytic anemia, in whom hematologic improvement did not occur during treatment with steroids but did ensue following splenectomy. In none of these did splenectomy exert a prejudicial effect upon the course of the underlying systemic lupus erythematosus during periods of observation ranging from one and a half to two and a half years. Two of the patients manifested an erythroblastopenic crisis while under close observation. The origin and role of erythroblastopenic crises in hemolytic states have been recently discussed [*5*].

CASE REPORTS

CASE 1. C. G. (Hosp. No. 5937F), a fifty-four year old Negro woman (Fig. 1), was seen in the outpatient clinic in 1949, with a twenty-five–year history of skin lesions of chronic discoid lupus erythematosus proved by skin biopsy. In November 1955 she noted the onset of weakness, easy fatiguability, evening fever, dyspnea on exertion, dark urine and stools, and loss of weight. These symptoms became increasingly severe in the few weeks prior to admission on September 8, 1956. By that time she had become bedridden, had lost 40 pounds, and was too weak to lift her arms.

Physical examination disclosed a temperature of 99.8°F., pulse 110, respirations 30, blood pressure 100/62 mm. Hg. The patient appeared pale, lethargic, weak and debilitated. Skin lesions typical of chronic discoid lupus erythematosus were present on her face, arms and scalp. The fundi exhibited multiple "cotton-wool" exudates and a few scattered hemorrhages. Prominent cervical lymph nodes were palpated. The left border of the heart was 12 cm. from the midsternal line, and grade 2 systolic murmurs were heard at all valve areas. The liver was palpated 3 cm. below the right costal margin and the spleen was palpated 1 cm. below the left costal margin.

The patient did poorly following admission, with a progressive fall in hemoglobin to 3.1 gm. per cent by September 9. She received 1,000 cc. of whole blood but in three days the hemoglobin level had fallen again to 3.6 gm. per cent. A bone marrow examination revealed an intense erythroid stimulation. A direct Coombs' test was positive. The report from the Venereal Disease Research Laboratories was positive. Leukocytes were consistently in the range of 3,000 to

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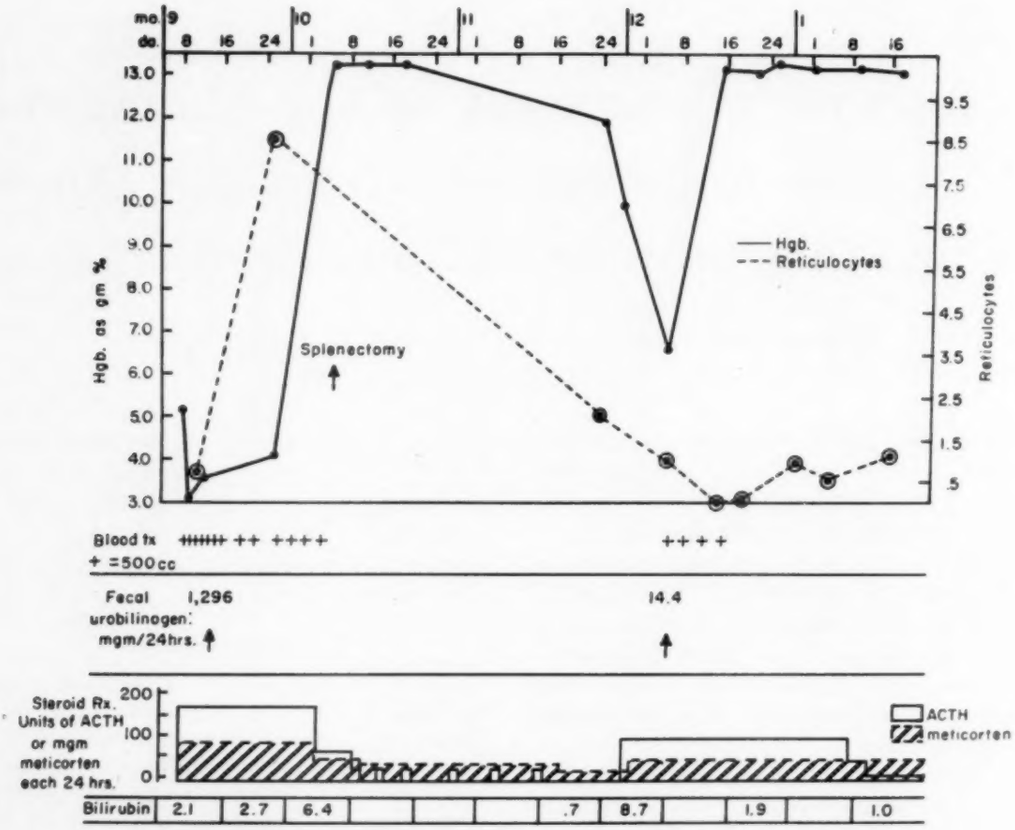
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ACTH
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FIG. 1. Summary of clinical course of patient C. G. (Case 1).

6,000/cu mm. On September 13 she was started on ACTH gel, 40 units intramuscularly every six hours, and Meticorten,® 30 mg. daily. Despite this therapy she required repeated blood transfusions (about 500 cc. every three days) to maintain the hemoglobin level above 5 gm. per cent. The temperature ranged between 100°F. and 103°F. until October 7 after which time it became normal. On October 5 splenectomy was performed. The spleen weighed 325 gm. and demonstrated collagenous degeneration and fibrosis consistent with lupus erythematosus. Also present was a splenic abscess which was ruptured during the procedure. Pus from the abscess was cultured and revealed the presence of paracolon bacilli. Postoperatively she received penicillin and streptomycin for seven days. Thereafter her course was satisfactory; she was afebrile and the hemoglobin level remained between 13.1 and 15.3 gm. per cent.

On October 17 she was discharged on maintenance steroid therapy: Meticorten, 15 mg. daily, and ACTH gel, 40 units weekly. On November 23 chills, fever and abdominal pain in the right upper quadrant associated with bile-stained vomitus occurred. She was readmitted on November 24. Blood cultures revealed paracolon bacilli on three successive examinations. This organism was sensitive to chloramphenicol. The temperature initially varied between 100°F. and 103°F., but fell to normal by December 15. The leukocyte count was elevated to 26,000 per cu. mm. with a marked left shift. This leukocytosis subsided by January 1, 1957. A chest film revealed the presence of right lower lobe pneumonia which disappeared during therapy. She was treated with chloramphenicol and penicillin with good response until December 5, 1956, when the hemoglobin level fell rapidly. Bone marrow examinations confirmed the impression of an erythroblastopenic crisis. At this point the steroid dosage was increased to 30 units of ACTH gel intramuscularly every six hours, and 40 mg. of Meticorten daily. The bone marrow regenerated slowly, and by December 16 the hemoglobin level remained stable. The patient was discharged on January 10, 1957, on maintenance steroid therapy, and has been seen in the clinic since then. The lupus erythematosus tests have been only suggestively positive. Severe hemolysis did not recur following splenectomy until December 1957 when steroid therapy was withdrawn and a severe hemolytic state promptly reappeared. Reinstitution of steroid therapy immediately brought the hemolysis under control. The last clinic visit was on February 11, 1958, and the disease was in remission at that time.

Comments: This case demonstrates the beneficial effect of splenectomy upon the autoimmune

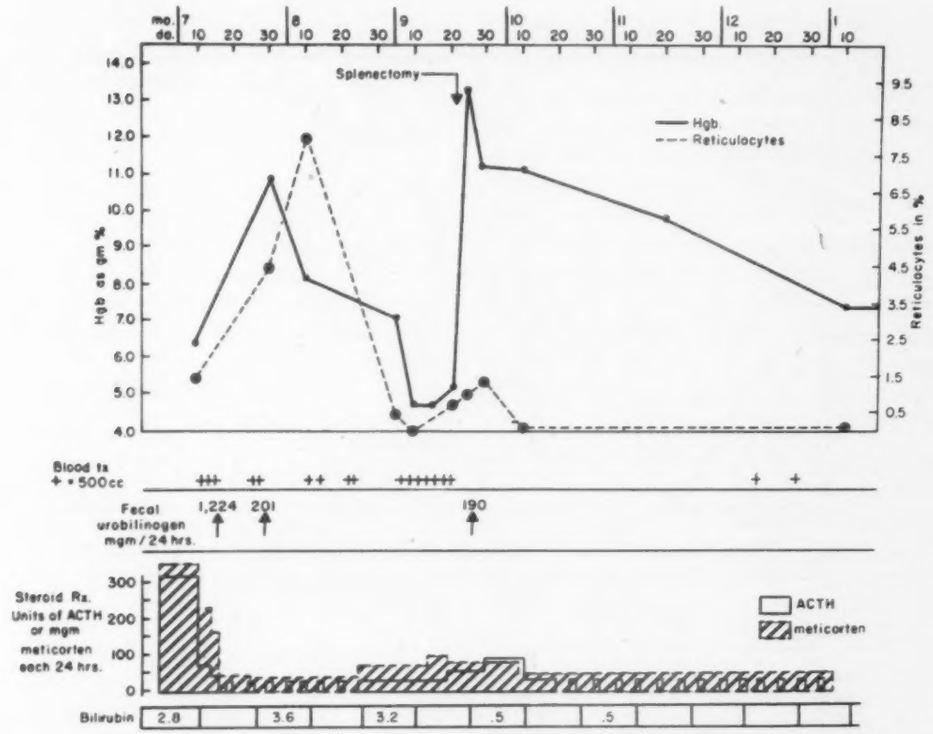

FIG. 2. Summary of clinical course of patient P. H. (Case II).

hemolytic anemia complicating systemic lupus erythematosus, although splenectomy did not protect the patient from an erythroblastopenic crisis. The course of the underlying systemic lupus erythematosus was not prejudiced by splenectomy.

CASE II. P. H. (Hosp. No. 27850-M), a thirty-one year old white woman (Fig. 2), noted the onset of mild pharyngitis and fever in May 1956, which was treated with penicillin and sulfonamides. In June 1956 arthralgia of the left knee and hip developed followed by some stiffness of these joints, malaise, low grade fever, weakness and icteric scleras. By late June she was admitted to a local hospital with high fever, jaundice and severe anemia; she was treated with blood transfusions and numerous antibiotics without improvement. The patient was transferred to John Sealy Hospital on July 11, 1956.

Physical examination disclosed a temperature of 100°F., pulse 120, blood pressure 120/60 mm. Hg. The patient was pale, weak, lethargic and toxic. The scleras were icteric. There was slight cardiomegaly with a loud snapping pulmonic second sound and a grade 2 systolic precordial murmur heard at all valve areas. The liver was palpated 4 cm. below the right costal margin and the spleen was palpated 5 cm. below the left costal margin. Both organs were quite firm. The feces were dark but not tarry.

During the next three days the temperature rose to 102°F., the pulse rate rose to 160, and a gallop rhythm was detected. The hemoglobin level had fallen rapidly despite blood transfusions. A bone marrow examination revealed the presence of an erythroblastopenic crisis. On July 14, ACTH was administered intravenously and cortisone was given orally in large doses. A dramatic response ensued with progressive rise in the hemoglobin level, slowing of the pulse rate, lysis of fever, and recession of the palpable liver and spleen. An erythrocyte survival time revealed a T½ of six days. A direct Coombs' test was positive. Steroid therapy was slowly decreased and by August 18 she was markedly improved. The patient was discharged on Meticorten, 40 mg. daily, and ACTH gel, 20 units intramuscularly twice weekly.

On August 30 she returned with progressive weakness and a temperature of 104°F. The hemoglobin level was 4.8 gm. per cent and the bone marrow revealed another erythroblastopenic crisis. Severe hemolysis was demonstrated. The hemoglobin level could not be maintained even after regeneration of the marrow, despite large doses of steroids.

On September 21 splenectomy was performed. The postoperative course was uneventful, and thereafter the hemoglobin level rose above 10.0 gm. per cent. On October 20 she was discharged on maintenance steroid therapy. She did well for two months, but for several months thereafter a slowly progressive fall in hemoglobin was noted, requiring 2 pints of blood each month. The lupus erythematosus tests have remained negative, and the platelet counts have always been within normal limits. Recurrent joint symptoms have

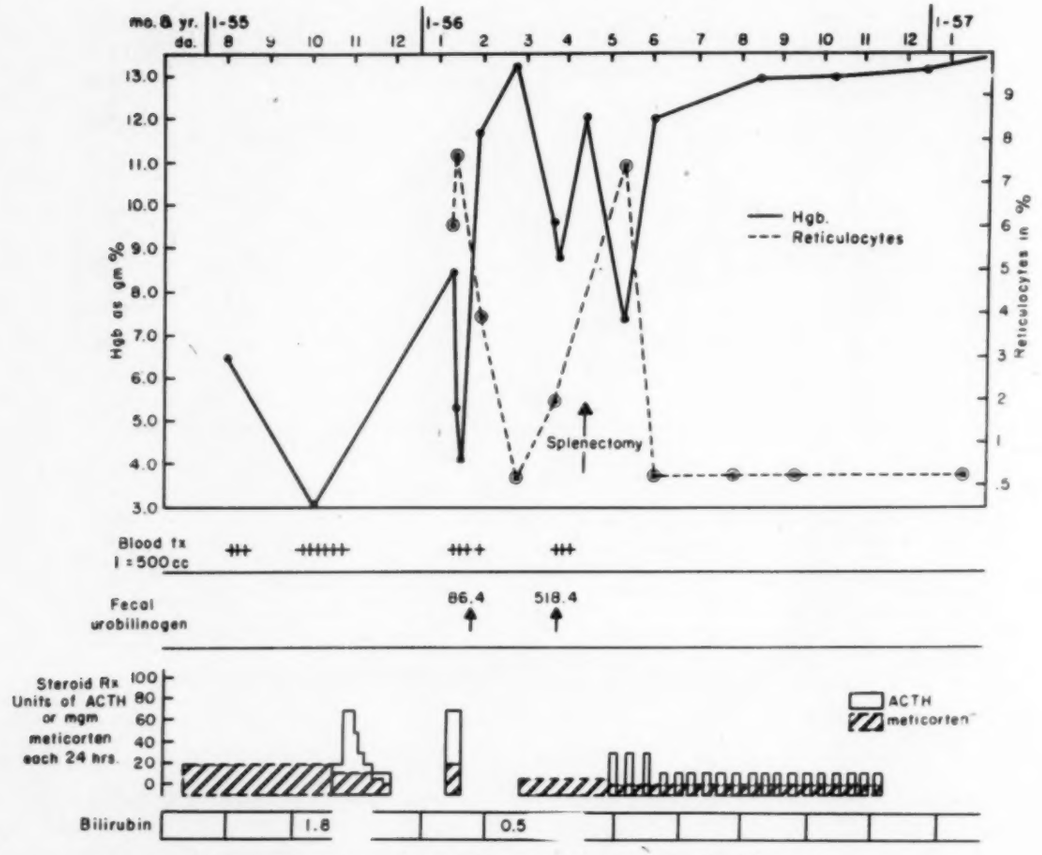

FIG. 3. Summary of clinical course of patient A. M. (Case III).

been experienced from time to time. The leukocyte levels were within the range of 7,000/cu. mm. Our pathologists were asked to review sections of the spleen. It is their opinion that the spleen in this case is compatible with such a clinical diagnosis. In December 1957 the patient reported by letter that she had gradually improved and no longer required steroid therapy or blood transfusions. A satisfactory hemoglobin level had persisted for some months without any further therapy.

Comments: This case demonstrates the value of splenectomy in controlling severe autoimmune hemolytic anemia without exerting a prejudicial effect on the underlying systemic lupus erythematosus. It also serves to emphasize the variable course of systemic lupus erythematosus. The patient is now in a quiescent period of the disease. The most severe erythroblastopenic crises occurred prior to splenectomy.

CASE III. A. M. (Hosp. No. 20543-M), a nineteen year old white girl (Fig. 3), noted the onset of fever, mild arthralgia with transient migratory joint stiffness, progressive weakness and jaundice in September 1955. Several recurrences of these symptoms were experienced, and during this time she was found to be sufficiently anemic to require blood transfusions. Her physician noted splenomegaly and instituted a regimen of Meticorten, 30 mg. daily, in October 1955. She did well until late in December 1955 when her symptoms recurred. She was referred to the John Sealy Hospital on January 13, 1956.

Examination disclosed a temperature of 99.2°F., pulse 96, blood pressure 100/60 mm. Hg. Extreme pallor, weakness and slight icterus were present. The spleen was palpable 2 cm. below the left costal margin.

Following admission the hemoglobin fell to 4.2 gm. per cent. A bone marrow examination revealed intense erythroid stimulation. She was treated with Meticorten, 30 mg. daily, and ACTH gel, 80 units daily, with a prompt response. These drugs were slowly withdrawn and there was no recurrence of the hemolytic anemia for three weeks. At the time of discharge on February 20, 1956, the direct Coombs' test was positive, the report from the Venereal Disease Research Laboratory was positive, and the cold hemagglutinin titer was positive in a titer of 1/80. On March 29, 1956, she was readmitted because of recurrent severe hemolytic anemia. At the time she complained of stiffness and pain in her wrists and shoulders. She failed to respond to reinstitution of

steroid therapy, and on April 13 splenectomy was performed. A good response was observed postoperatively and she was discharged on April 21, requiring no steroid therapy.

During the following months the hemoglobin level began to fall slowly and the hemolytic state recurred. At that time maintenance steroid therapy was reinstituted with a good response. She remained asymptomatic, except for a brief episode of mild polyarthritis during June 1956. Two positive lupus erythematosus tests were obtained in the last twelve months. She was last seen in the Hematology Clinic on February 24, 1958, and was asymptomatic. Steroid maintenance therapy is being continued.

Comments: This case again demonstrates the value of splenectomy in controlling autoimmune hemolytic anemia. The initial demonstration of a positive lupus erythematosus test following splenectomy is not evidence of an adverse effect since the patient's clinical state has remained essentially normal.

COMMENTS

Mechanism of Production of Acquired Hemolytic Anemia in Systemic Lupus Erythematosus. Autoimmunization: Autoimmunization plays a prominent role in the pathogenesis of acquired hemolytic anemia complicating systemic lupus erythematosus although the mechanism of formation of antierythrocyte antibodies remains obscure. Wasserman et al. [*3*] have recently reviewed this subject and propose the following possible mechanisms for autoantibody production: (1) Hyperplasia of the reticuloendothelial system and lymphatic tissues in systemic lupus erythematosus may lead to overproduction and abnormal character of antibodies. (2) Autoantibody production may be just another manifestation of disordered protein metabolism found in systemic lupus erythematosus. (3) Cross reactivity due to antigens found in nature that are similar to the blood group antigens may produce antibodies that will react with the blood group antigens. (4) Repeated stimulation with an antigen may in time lead to formation of antibodies which lose their specificity for the original antigen and will react with one of the blood group antigens [*3*].

Role of the spleen: Although most of the accumulated evidence regarding the pathogenesis of acquired hemolytic anemia complicating systemic lupus erythematosus incriminates autoantibodies as responsible for the hemolysis, other factors are involved. This is supported by studies which have shown that erythrocytes coated with autoantibodies transfused into normal recipients may survive normally [*6*]. Much of the controversy related to the pathogenesis and treatment of acquired hemolytic anemia complicating systemic lupus erythematosus is centered about splenic function.

In the uncommon type of acquired hemolytic anemia in which the erythrocytes appear to be uninjured by autoantibodies, an abnormal hypersplenic mechanism may be responsible for the hemolytic anemia. Dameshek and Estren have postulated that the spleen exerts an inhibitory effect on the bone marrow which can lead to one or more cytopenias. This is supported by the observation that such patients experience a sustained remission following splenectomy [*7*].

In acquired hemolytic anemia, Doan and Wright suggest that the macrophages in the spleen phagocytize the cellular elements of the peripheral blood in excessive amounts when splenomegaly is present [*8*]. Dubois also suggested that acquired hemolytic anemia complicating systemic lupus erythematosus is due to involvement of the spleen by lesions of lupus erythematosus, leading to a secondary hypersplenism [*9–10*]. Johansen postulated that the spleen resorbs a plasma factor which promotes marrow function and that this phenomenon is exaggerated in hypersplenic states [*11*].

Another possible mechanism of hypersplenism involves the spleen as a site of antibody production. Evans proposed that splenectomy may produce a reduction of antibody formation to below a critical level. Relapses would indicate that extrasplenic reticuloendothelial structures have accelerated their production of autoantibodies [*12*].

It is probable that all of the mechanisms are interrelated and serve as multiple factors in the genesis of anemia. On the one hand there are examples of hypersplenism with little or no evidence of autoantibody formation, while other patients possess high titers of autoantibodies with little evidence of hypersplenism. Multiple factors doubtless are operative in the production of acquired hemolytic anemia complicating systemic lupus erythematosus. In these cases the spleen has the dual role of being a major site of autoantibody production and a major site of destruction of sensitized red blood cells [*3,13*].

Effects of Splenectomy in General. Following removal of the normal spleen, other elements of the reticuloendothelial system compensate so

well that information of normal splenic physiology has been difficult to obtain. Removal of a normal spleen has no significant effect on the health or longevity of an adult [*14*], although certain alterations of the peripheral blood picture do occur. Suggested potential effects of splenectomy are based upon the known functions of the normal spleen which include the following:

1. Changes in the peripheral blood following splenectomy may include thrombocytosis, granulocytosis, eosinophilia, lymphocytosis, monocytosis, mild transient anemia, reticulocytosis and the presence of Howell-Jolly bodies in the erythrocytes. The marrow may even be hyperplastic. All of these changes are thought to be related to the role of the spleen in regulating hematopoiesis [*15*].

2. The spleen may serve as a reservoir of red blood cells which can be delivered to the peripheral circulation in time of emergency [*16*]. In man this function is not prominent [*15*].

3. The spleen may be a site of extramedullary hematopoiesis in the adult when the capacity of the bone marrow is exceeded by demands imposed by hemolysis or hemorrhage [*15*].

4. The function of orderly destruction of senile or effete erythrocytes is adequately compensated by other reticuloendothelial structures in the absence of the spleen [*15*].

5. Following splenectomy the defense mechanisms of the body may be impaired. There is certainly a deficit in antibody production at least in the initial postsplenectomy period [*17*]. However, in adults there is no evidence that persons who have undergone splenectomy have increased susceptibility to infection or to the development of malignancy [*15*]. In children who have undergone splenectomy, decreased resistance to infection has been demonstrated [*18*].

Effect of Splenectomy in Patients with Systemic Lupus Erythematosus. There is a divergence of opinion regarding the effect of splenectomy upon the course of systemic lupus erythematosus. In any such evaluation the fact that systemic lupus erythematosus is not necessarily a rapidly and progressively fatal disease is an important consideration. Its course may be one of spontaneous remissions and exacerbations with periods free of detectable disease [*19*]. A similar cyclic course may also characterize acquired autoimmune hemolytic anemia [*3*]. The lupus erythematosus test cannot be accepted as an infallible indicator of the presence of systemic lupus erythematosus. Furthermore, there is no dependable correlation between the positivity of this test and the severity of a case of lupus erythematosus [*20*].

Dameshek has postulated that the spleen exerts an inhibitory effect on the course of lupus erythematosus and that splenectomy may lead to activation of a previously latent systemic lupus erythematosus [*4*]. Other authors have reported that splenectomy was without benefit in patients with systemic lupus erythematosus complicated by acquired autoimmune hemolytic anemia [*20*]. These opinions may produce hesitancy in recommending splenectomy in any patient with autoimmune hemolytic anemia or thrombocytopenic purpura, for in any of these there may be an underlying "latent" systemic lupus erythematosus. This policy is exemplified by the report of a case of autoimmune hemolytic anemia in which splenectomy was not performed because a diagnosis of systemic lupus erythematosus could not be excluded [*21*]. On the other hand, there are reports which indicate that the hemolytic process may be ameliorated by splenectomy without affecting the course of the underlying lupus erythematosus [*2,9,22,23*]. In almost all patients with autoimmune hemolytic anemia, splenectomy produces some diminution in the rate of hemolysis. If the rate of hemolysis greatly exceeded the functional limit of erythropoiesis before surgery, a modest increase in erythrocyte survival is of no clinical benefit [*13*].

Recommendations for Management of Autoimmune Hemolytic Anemia Complicating Systemic Lupus Erythematosus. It is recommended that patients with acquired autoimmune hemolytic anemia, complicating systemic lupus erythematosus, should be managed in the same fashion as patients with idiopathic autoimmune hemolytic anemia. The regimen suggested includes the following measures:

Blood transfusions: In patients with severe anemia, transfusions may be life-saving, despite the fact that transfusion reactions readily develop in these patients. Even when the greatest care is used in selecting blood for transfusion, they may still have a "plasma reaction." Dameshek recommends administering 20 cc. of the intended donor's plasma intravenously to the intended recipient to determine whether the patient is sensitive. If fever, chills and/or joint pain should develop following the intravenous administration of the donor's plasma, the donor's red cells should be washed three times before administra-

tion [7]. Under any circumstances, packed erythrocytes are preferable to whole blood.

Steroid therapy: Since Hench's report in 1949 of the therapeutic value of ACTH and cortisone in systemic lupus erythematosus [*24*], these two drugs have proved to be the most effective form of palliative therapy. When acquired hemolytic anemia complicates systemic lupus erythematosus, steroid therapy is still the therapy of choice [*9,14,20,22*]. Many dosage levels and schedules have been proposed, but a generally accepted program of 400 mg. of cortisone (or its equivalent in one of the newer corticoids) or 150 units of ACTH daily in divided doses can be employed initially. Some authors prefer to use both drugs simultaneously. If there is a response to this therapy, the dosage is gradually reduced to a minimum maintenance level. Larger dosages are given if there is no response.

Splenectomy: Patients who do not show an adequate response to the preceding therapeutic recommendations should, in our opinion, undergo splenectomy. The patients reported herein have doubtless had extension of life expectancy as well as reduction in the hemolytic process as a result of splenectomy. In all three patients the ravages of autoimmune hemolytic anemia were even more intense that those of systemic lupus erythematosus. In all instances following splenectomy the hemolytic states have become partially or wholly compensated. Splenectomy appears in no instance to have exerted a prejudicial effect upon the course of systemic lupus erythematosus.

Other forms of therapy: In the event that a patient should not respond to all of the preceding recommendations, maintenance of the hemoglobin level would have to be accomplished by blood transfusions. It has been reported that some patients with idiopathic autoimmune hemolytic anemia who fail to respond to steroid therapy and splenectomy subsequently respond to nitrogen mustard therapy.

Intravenous administration of colloidal radioactive gold: This has produced a similar desirable effect [*25*]. No report was found in which these measures were used in patients with systemic lupus erythematosus.

SUMMARY AND CONCLUSIONS

The mechanisms of autoimmune acquired hemolytic anemia in systemic lupus erythematosus are reviewed.

Previous reports have suggested that splenectomy is contraindicated in the treatment of the acquired hemolytic anemia complicating systemic lupus erythematosus because of a prejudicial effect on the course of systemic lupus erythematosus. The clinical experience reported in this paper does not support this view. Such patients should have an initial vigorous trial of steroid therapy but in the event that the hemolytic state is not satisfactorily controlled splenectomy should be performed.

ADDENDUM

Eight months have elapsed since the preparation of this manuscript. During this period of time the patients reported herein have continued to improve. The patient in Case I requires small daily doses of steroids, the patient in Case II is taking no medication and has required no blood transfusions for twelve months, and the patient in Case III is completely asymptomatic, being maintained on moderate doses of prednisone. Hematologic compensation appears to be complete in all three instances, and the manifestations of systemic lupus erythematosus are minimal or absent.

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Infectious Hepatitis in Clearfield County, Pennsylvania*

I. A Probable Water-Borne Epidemic

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DURING March 1956 the Clearfield County Medical Director reported to the Pennsylvania Department of Health that cases of infectious hepatitis were occurring in and around the town of Curwensville. During that month the number of cases increased rapidly, and it became obvious that an epidemic was occurring. The disease was sufficiently prevalent during the latter part of March to make it advisable to give immune globulin on a community-wide basis.

An investigation of the epidemic was carried out by the Pennsylvania Department of Health and the Hepatitis Investigations Unit, Communicable Disease Center, Public Health Service. It was found that 189 cases had occurred among children and adults in Curwensville and the surrounding area during a thirty-nine-day period. Analysis of the data concerning these cases suggested a common source epidemic with the municipal water supply as the probable vehicle.

While a number of water-borne outbreaks of infectious hepatitis have been reported previously, only five were attributed to municipal supplies [*1–5*]. It is believed that the data obtained are of sufficient interest to be summarized in this report.

DESCRIPTION OF THE AREA

Clearfield County is located in the west-central area of Pennsylvania. The population at the time of the 1950 census was 85,957. Since that time there has been an estimated increase to 92,000.

The town of Curwensville, the focus of the epidemic, is located on the Susquehanna River in the central area of the County. It is an incorporated borough which had a population of 3,332 at the time of the 1950 census. On survey, the population at the time of the epidemic was found to be 3,028. There are three elementary schools in Curwensville, and a Joint School which includes the seventh through the twelfth grades. Curwensville and part of the immediately surrounding area are served by a municipal water supply, which is privately owned. There is a sewer system, but it does not serve the entire community.

The epidemic also involved the contiguous area which comprises the Curwensville School Jointure. This includes the Boroughs of Grampian and Lumber City, and Ferguson, Greenwood, Penn and Pike townships. The population of the School Jointure in 1950 was 4,601. All children in this area in the seventh through twelfth grades attend the Joint School in Curwensville. In addition, many children in the lower grades attend one of the grammar schools in Curwensville. A number of adults living in the area of the School Jointure are employed in Curwensville.

METHOD OF STUDY

Information concerning suspected cases was obtained in three ways: (1) Reports to the Health Departments by physicians in the County. (2) Canvassing of the schools in Curwensville. (3) A house-to-house survey in Curwensville, described herein. Each person reported or suspected of having infectious hepatitis was visited by a public health nurse or a physician, and a clinical and epidemiologic history of

* From the Department of Health, Commonwealth of Pennsylvania, and the Hepatitis Investigations Unit, Epidemiology Branch, Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare.

TABLE 1
CASES OF INFECTIOUS HEPATITIS
CLEARFIELD COUNTY, PENNSYLVANIA
(JANUARY THROUGH JUNE, 1956)

Month	Borough of Curwensville (Pop. 3,332)	School Jointure Exclusive of Curwensville (Pop. 4,601)	County Exclusive of Curwensville and Jointure (Pop. 78,024)	Total (Pop. 85,957)
January	0	2	12	14
February	4	2	6	12
March	107	38	16*	161
April	26	5	19	50
May	4	1	8	13
June	0	0	7	7
Total	141	48	68	257
Rate per 1,000†	42.3	10.4	0.9	3.0

* Includes one case in which date of onset in March was indefinite.
† For the six-month period.

the illness was obtained. Charts of all hospitalized patients were reviewed for additional information.

By the time the investigation was begun the epidemic had subsided. It was not possible, therefore, to visit the majority of patients during the acute phase to carry out a physical examination or obtain blood for laboratory studies indicative of hepatic dysfunction. A reliable diagnosis of anicteric infections therefore could not be made. The criteria adopted for inclusion of a case in the study were: (1) an acute illness characterized by definite jaundice, either scleral or generalized, and (2) an otherwise compatible history.

Ten of the patients reported by physicians from Curwensville and the rest of the School Jointure were not jaundiced. Since the recognition and reporting of anicteric cases is not uniform and since suspected anicteric infections found on survey had to be excluded, the reported anicteric cases were excluded to afford maximal comparability of the epidemiologic data.

From the information immediately available on reported cases it was believed that the outbreak in Curwensville and the immediately surrounding area had the characteristics of a common source epidemic. In order to obtain information on environmental factors which could be of significance, a house-to-house survey of the entire community was carried out. The information gathered included: name, sex, age, place of work or school attended, immunization with globulin, and history of jaundice during 1956 for each person in the household, and the source of water and type of sewerage for the household.

For the survey, the Borough of Curwensville was divided into sections based largely on the topography of the area. Each section was subdivided into blocks, and all dwelling units plotted. As many visits as necessary were made to each unit to obtain the information desired. Household lists obtained from the survey were checked against the telephone directory, school census data, and the delivery list of the largest dairy. It is believed that virtual completeness was obtained, although the population figure obtained was 310 less than the 1950 census. In addition, the survey was extended to those areas immediately adjacent to the Borough served by the municipal water supply.

CLINICAL CHARACTERISTICS

A total of 189 cases from Curwensville and the rest of the School Jointure during the period January through June 1956, fulfilled the criteria given. The impression of physicians was that the infection generally was mild and that recovery in almost all instances was prompt. There were no deaths attributed to hepatitis.

Forty-seven, or 25 per cent, of the patients were hospitalized. The length of hospitalization ranged from three to fifteen days, with a mean of 7.9 days. Leukocyte counts for hospitalized patients ranged from 4,000 to 11,600 per cu. mm., with a mean of 5,900. Twenty-eight counts (60 per cent) were below 6,000 per cu. mm.; one was over 10,000. Quantitative serum bilirubin determinations were carried out in thirty-three cases. The highest value recorded ranged from 3.2 to 15.0 mg. per cent, with a mean of 6.0. Tests for complement-fixing antibodies to Leptospira icterohemorrhagica, pomona and canicola were carried out with serums from six patients

convalescing from the disease. Antibodies were absent from all serums.

EPIDEMIOLOGIC FEATURES

The number of confirmed cases of infectious hepatitis in Clearfield County each month during the period January through June 1956, is indicated in Table I. This table is subdivided to show the number of cases in three geographic areas within the County: (1) the Borough of Curwensville; (2) the Curwensville School Jointure exclusive of the Borough of Curwensville; and (3) the rest of the County exclusive of these two subdivisions. It may be seen that 141 cases occurred in Curwensville, and 48 in the rest of the School Jointure, representing rates of 42.3 and 10.4 per 1,000, respectively, for the six month period, if 1950 census data are used. This compares with the rate of 0.9 per 1,000 in the rest of the County during the same period. While rates are not strictly comparable because of the case-finding survey in Curwensville, reporting by physicians during this period was good and the difference in magnitude is probably of approximately this order.

This is illustrated in Figure 1 which gives the onset for each case during this period in the three areas. It may be seen that while there were scattered cases throughout the period in the rest of the County, there were few cases in Curwensville and the School Jointure except during the epidemic period in March, extending into early April in Curwensville. It is obvious from this that the Curwensville and School Jointure areas were the focus of the disease.

Early Cases. Infectious hepatitis began to occur in the area of the Curwensville School Jointure about eleven weeks prior to the beginning of the epidemic. The first known illness was the unreported case of a six year old boy, R. B., who attended the first grade at the Locust School in Curwensville. Symptoms developed on December 12, 1956, and he had a typical illness with generalized jaundice.

On January 14, 1956, thirty-three days later, H. H., a six year old boy in the same classroom as R. B., became ill with icteric hepatitis. On February 5, twenty-two days after the onset of H. H.'s illness, his mother, C. H., became ill and icteric hepatitis developed. The time relationships of the illnesses of H. H. and C. H. will be discussed later.

There were six other illnesses from infectious hepatitis in Curwensville and the School Jointure during January and February, as may be seen on the left in Figure 1. Five were school children; the sixth was a forty-three year old man. These were widely scattered in the community.

Thus, infectious hepatitis began occurring in the area almost three months before the epidemic, but only as occasional, sporadic cases.

THE EPIDEMIC PERIOD

One hundred and twenty-nine of 141 cases in the Borough, and forty of forty-eight cases in the rest of the School Jointure occurred during the thirty-nine-day period from March 2 through April 9. The definition of an epidemic period must be arbitrary but, as may be seen from Figure 1, this thirty-nine-day period approximates the limits of the epidemic curve.

The form of the epidemic curve is more completely delineated for the Borough than the rest of the School Jointure because of the larger number of cases. The first case in the Borough during the epidemic period occurred on March 4; the largest number of cases (twelve) occurred on March 28, twenty-four days later. Only eight cases occurred after April 9. In the rest of the School Jointure, most of the cases occurred between March 17 and March 28, with the largest number (six) on March 21. The similarity of the distribution in time of the cases in the rest of the School Jointure to that in the Borough is interpreted as indicating that the behavior of the disease in these two areas was epidemiologically related. There are further reasons for assuming this, as will be discussed subsequently.

In relation to the form of the epidemic curve, it should be noted that immune globulin was given to approximately 2,800 persons on March 26 and 27. This may have been largely responsible for the decline in the number of cases thereafter, although forty cases occurred in persons who had received immune globulin one to nineteen days prior to onset.

Age Distribution. Table II shows the age and sex distribution of cases during the epidemic period. In Curwensville, 94.6 per cent of the cases occurred in persons between five and thirty-nine years of age, with 60.5 per cent in persons between five and nineteen years of age, and 34.1 per cent in those between twenty and thirty-nine. The age distribution in the rest of the School Jointure differs, with 80.5 per cent of the cases occurring in persons between five and nineteen years of age. It may be seen, therefore,

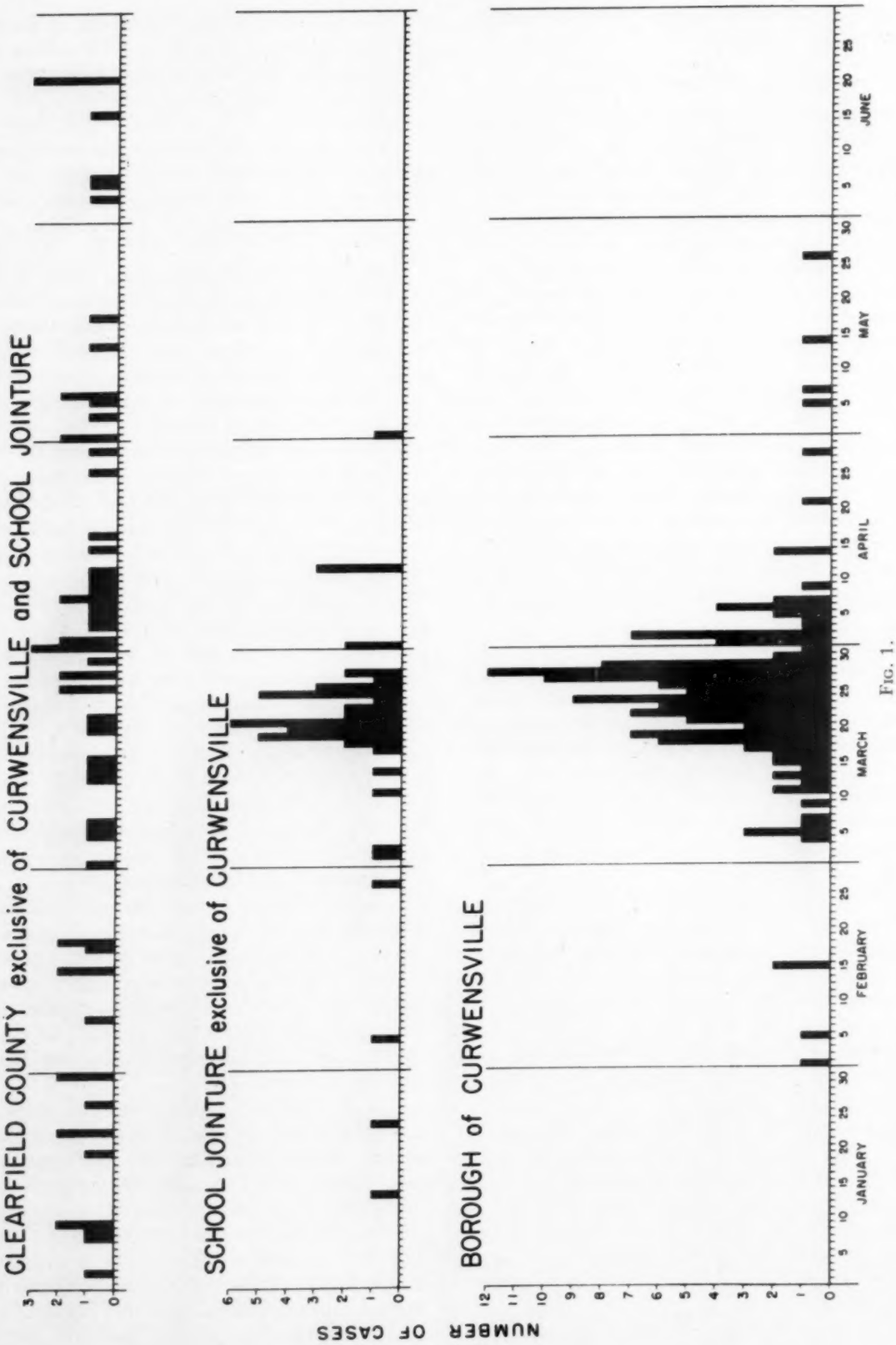
CLEARFIELD COUNTY exclusive of CURWENSVILLE and SCHOOL JOINTURE
SCHOOL JOINTURE exclusive of CURWENSVILLE
BOROUGH of CURWENSVILLE
NUMBER OF CASES
JANUARY
FEBRUARY
MARCH
APRIL
MAY
JUNE

FIG. 1.

TABLE II
SEX AND AGE DISTRIBUTION
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

Age Group	Borough of Curwensville				School Jointure Exclusive of Curwensville			
	Male	Female	Total	% Total	Male	Female	Total	% Total
Less than 5	2	1	3	2.3	0	1	1	2.4
5–9	10	10	20	15.5	7	1	8	19.5
10–14	13	12	25	19.4	8	8	16	39.0
15–19	25	8	33	25.6	7	2	9	22.0
20–29	9	14	23	17.8	2	3	5	12.2
30–39	13	8	21	16.3	0	0	0	0.0
40–49	1	2	3	2.3	2	0	2	4.9
50–59	1	0	1	0.8	0	0	0	0.0
60 and over	0	0	0	0.0	0	0	0	0.0
Total	74	55	129	100.0	26	15	41	100.0

that the epidemic within the Borough involved both children of school age and younger adults, while outside the Borough it was largely confined to children of school age.

Table III shows the age-specific attack rates for Curwensville. The attack rate is high between the ages five and thirty-nine, with the highest rate (16.0 per cent) in the fifteen to nineteen year old group. Population data for the rest of the School Jointure for calculation of age-specific attack rates were not available.

Sex Distribution. From Table II it may be seen that there was a preponderance of males, both in the Borough and the rest of the School Jointure. The reason for this is not apparent.

TABLE III
AGE-SPECIFIC ATTACK RATES
CASES OF INFECTIOUS HEPATITIS
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

Borough of Curwensville			
Age Group	Population from Census*	Cases	Rate per 100†
Less than 5	281	3	1.07
5–9	319	20	6.27
10–14	263	25	9.50
15–19	206	33	16.0
20–29	277	23	8.30
30–39	444	21	4.73
40–49	471	3	0.64
50–59	273	1	0.37
60 and over	470	0	0.00
Not given	20	0	.....
Total	3,024	129	4.27

* Excludes four cases prior to epidemic period as non-susceptibles.

† Rate for the thirty-nine-day period only.

TABLE IV
ATTACK RATE BY SURVEY SECTIONS
CASES OF INFECTIOUS HEPATITIS
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

Section	Population	Cases	Attack Rate per 100
Survey Sections within Borough of Curwensville			
A	222	0	0.0
B	206	2	1.0
C	239	20	8.4
D	210	3	1.4
E	284	19	6.7
F	331	14	4.2
G	222	3	1.4
H	905	45	5.0
I	357	22	6.2
J	48	1	2.1
Total	3024	129	4.3
Survey Sections outside Borough of Curwensville			
K	76	1	1.3
L	203	14	6.9
Total	279	15	5.4

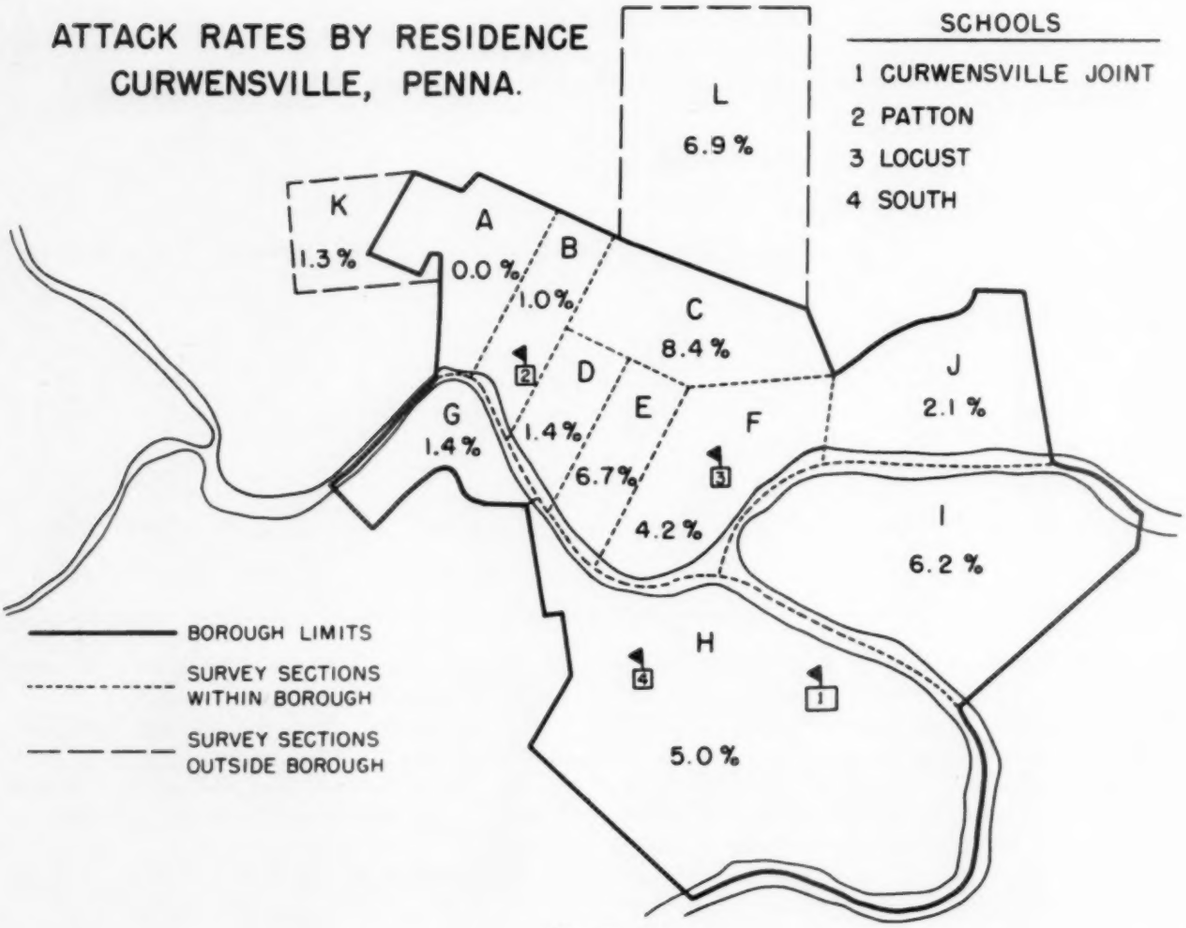

FIG. 2.

Geographic Distribution. From plotting of cases in the Borough of Curwensville it became evident that they were concentrated in several sections, while other sections were relatively spared. Table IV gives the number of cases and attack rates during the epidemic period. Attack rates varied from 0.0 per cent to 8.4 per cent. One sees from Figure 2 that in the sections on the west side of the community (A, B, D, G and K) the rate was low, being from 0.0 to 1.4 per cent, while in

TABLE V

ATTACK RATES IN CURWENSVILLE SCHOOLS
CASES OF INFECTIOUS HEPATITIS
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

School	Grades Included	Borough of Curwensville			Rest of School Jointure		
		Students	Cases	Rate per 100	Students	Cases	Rate per 100
Joint School	7th–12th	286	35	12.2	531	20	3.76
Patton School	1st–6th	171	10	5.8	66	1	1.5
Locust School	1st–6th	110	17	15.4	130	11	8.5
South School	1st–4th	78	6	7.6	45	1	....
Total	.....	645	68	10.5	772	33	4.27

those on the east side of the community (C, E, F, H, I and L) the rate was high, varying from 4.2 to 8.4 per cent. The only exception is section J, in which the rate was 2.1 per cent.

Cases in the Curwensville School. Table v shows the attack rates for the four schools in Curwensville, with subdivisions of the students from the Borough and from the rest of the School Jointure. It may be seen that during the epidemic period icteric hepatitis developed in 10.5 per cent of the students from Curwensville, and in 4.27 per cent of those from the rest of the School Jointure attending Curwensville schools.

POSSIBLE COMMON SOURCES

Consideration was given to the possibility of a common source vehicle and the following information obtained.

Gatherings. On March 9 and 10 a district wrestling meet was held at the Curwensville Joint School which was attended by several hundred persons from the County, largely high school boys and adult males. It is thought that this could not have served as an occasion for common-source spread since it occurred after the beginning of the epidemic curve. Further, few of the patients questioned concerning attendance at the wrestling meet had been present.

The only other activities known were the high school basketball games which were attended only by a small percentage of the high school students and few adults or younger persons. There were no large church or social functions in the community, nor were the cases confined predominantly to any religious denomination or socio-economic group.

Food. There are several small restaurants and cafes in Curwensville at which food is prepared and served to the public. While occasionally food may be taken in other homes during a social visit, most persons in this small community eat at home. For those not able to return home at noon, lunches are usually carried. Few of the patients gave a history of eating in any of the public places.

At the time of the epidemic a school lunch program was in operation at the Locust School. There was no central cafeteria for the school and the lunches served were taken by the children to their respective classrooms to be eaten. Children at the other schools either returned home at noon or carried a lunch from home.

Milk. Households receiving milk by delivery in Curwensville and the immediate surrounding area are supplied almost exclusively by two dairies (A and B). A third dairy (C) contributes to the supply only through wholesale deliveries to retail outlets.

TABLE VI
MILK SUPPLY
CASES OF INFECTIOUS HEPATITIS
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

	Borough of Curwensville		Rest of School Jointure		Total	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Dairy A.....	91	70	5	31	96	66
Dairy B.....	27	21	5	31	32	22
Dairy C.....	12	9	2	12	14	10
Other.....	8	6	6	38	14	10
Total*....	129	100	16	100	145	100

* Total is less than sum of cases using each supply since several patients were exposed to more than one of the supplies.

Table VI presents the milk supply of the patients during the epidemic period. Dairy A supplied milk to 70 per cent of the patients in the Borough of Curwensville. This obviously required further investigation, and additional information was obtained. Dairy A at approximately one month after the epidemic period had 484 delivery customers among the 933 households within the Borough limits, so that 51.8 per cent of homes were supplied in this way. In addition, Dairy A supplied approximately 40 per cent of the milk sold through retail outlets in Curwensville. Therefore, the number of patients consuming milk from Dairy A is not beyond what would be expected. Further, the percentage of households served is more or less uniform throughout the Borough. There are two delivery routes, one including sections A, B, C, I and L, and the other D, E, F and H, so that the distribution of cases does not conform to this either. In addition, Dairy A supplied Patton School which had the lowest attack rate, but not Locust School which had the highest.

The sources and distribution of milk, therefore, do not account for the epidemiologic characteristics of the outbreak.

Water. The possibility of water-borne dissemination was investigated and found to offer the most probable explanation for the epidemio-

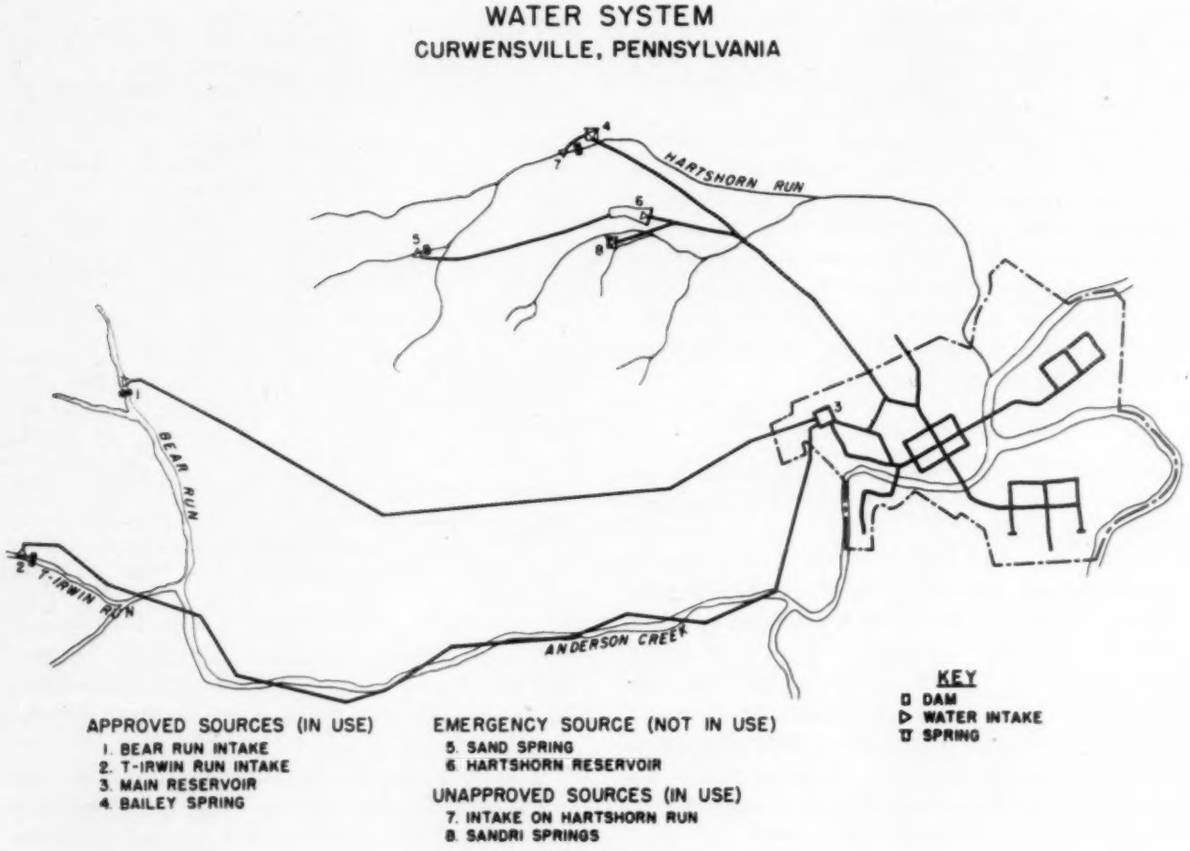

FIG. 3.

logic characteristics of the cases in Curwensville and the rest of the School Jointure.

THE CURWENSVILLE WATER SUPPLY

The water supply of Curwensville is provided by a privately owned company. The principal reservoir is located within the Borough limits and is fed by two 6 inch pipes which convey water from two streams in a privately owned watershed some four miles distant. (Fig. 3.) The watershed is uninhabited except for hunting camps, which are occupied only during the hunting season. During the winter months this area is largely inaccessible.

The water supplied by these streams is of excellent quality with no turbidity. This supply was chlorinated by means of an injector apparatus in one of the two mains carrying the raw water; the water from the second main was chlorinated by mixing with the other in the reservoir. The amount of chlorination and the period of detention, which was at least six hours, are considered to have been probably adequate for inactivation of the virus of infectious hepatitis, should such contamination have occurred [6]. The possibility of short-circuiting due to currents in the reservoir was considered but was thought to be unlikely.

The chlorinated water is conveyed from the reservoir into the community by two 6 inch mains which join as indicated in Figure 3.

A third approved source of water is Bailey Spring, located approximately three miles directly north of the community. (Fig. 3.) This is a spring which supplies water without turbidity or evidence of contamination on chemical analysis, and which has been negative for coliform organisms on culture at all times at which it was tested previously. The water from this source is conveyed through a 6 inch pipe into the town. As may be seen, it forms a continuous system with the water supply from the other mains.

On investigation it was found that in addition to water from Bailey Spring itself this main was also conveying water from two additional sources, both unapproved:

(1) A small dam and intake built on Hartshorne Run, with a 4 inch pipe which conveyed

TABLE VII
DATA ON WATER SOURCES
CURWENSVILLE WATER COMPANY
CLEARFIELD COUNTY, PENNSYLVANIA

	Turbidity	Ammonia (ppm)	Albuminoid (ppm)	Nitrite (ppm)	Nitrate (ppm)	Solids	Cultures Coliform Organisms (MPN)
Approved Sources							
T — Irwin Run	0	.008	.020	.000	.0	25	38
Bear Run	0	.006	.026	.000	.0	25	Negative
Main Reservoir	0	.006	.030	.000	.0	25	Negative
Bailey Spring	0	.006	.018	.000	.1	35	Negative
Unapproved Sources							
Sandri Springs	0	.006	.024	.000	.6	45	240 plus
Hartshorne Run	0	.006	.020	.000	.0	30	240 plus

water into Bailey Spring. (Fig. 3.) Chemical analysis of this source was satisfactory, but on culture a significant number of Escherichia coli were found.

(2) In addition, the pipe from Sandri Springs which had previously emptied into Hartshorne Reservoir had been relaid and joined to the main below Hartshorne Reservoir, so that it too emptied into the supply from Bailey Spring. (Fig. 3.) Cultures of this source also were positive for Esch. coli.

Table VII summarizes the results of sanitary chemical analyses and cultures of samples from the six sources in use at the time of the epidemic. Two contaminated systems were supplying water to the community through the mains from Bailey Spring.

To document this contamination further, ninety water samples were obtained from taps in homes on the public supply and cultures were run using the membrane filter technic. Of these, fourteen, or 16 per cent, were positive for coliform organisms. The distribution of positive and negative cultures by section and in relation to the water sources is shown in Figure 4. All positive samples were from sections C, E, F and L, that is, those areas probably served most directly by the Bailey Spring system. The unapproved sources were excluded from the water system on April 20, and, following this, cultures from taps in houses on the public supply which previously had been positive were repeated. All cultures then were found to be negative. It therefore seems very probable that these two sources account for the coliform organisms found in the municipal supply.

Bailey Spring is 43 feet higher than the main reservoir. Since the mains are interconnected in the downtown area, the distribution of water from the two sources would depend upon relative demand in the various areas.

DISTRIBUTION OF CASES IN CURWENSVILLE IN RELATION TO WATER SUPPLY

It became evident that a careful plotting of cases in relation to the water distribution system was necessary, and the detailed survey described previously was carried out, permitting exact determination of attack rates in relation to location in the community.

Sections C and L probably derived their water supply entirely from the Bailey Spring main, and persons in the households served in this area would be most heavily exposed to any contamination from this source. While the connection from one of the two mains carrying the chlorinated supply from the reservoir could in part supply section C, this is unlikely since Bailey Spring is 43 feet higher than the reservoir. These two sections experienced the highest attack rates, with 8.4 per cent and 6.9 per cent of their populations, respectively, becoming ill during the thirty-nine-day epidemic period.

Sections E and F lie on either side of the Bailey Spring main in the downtown area. Here the Bailey Spring system connects with mains

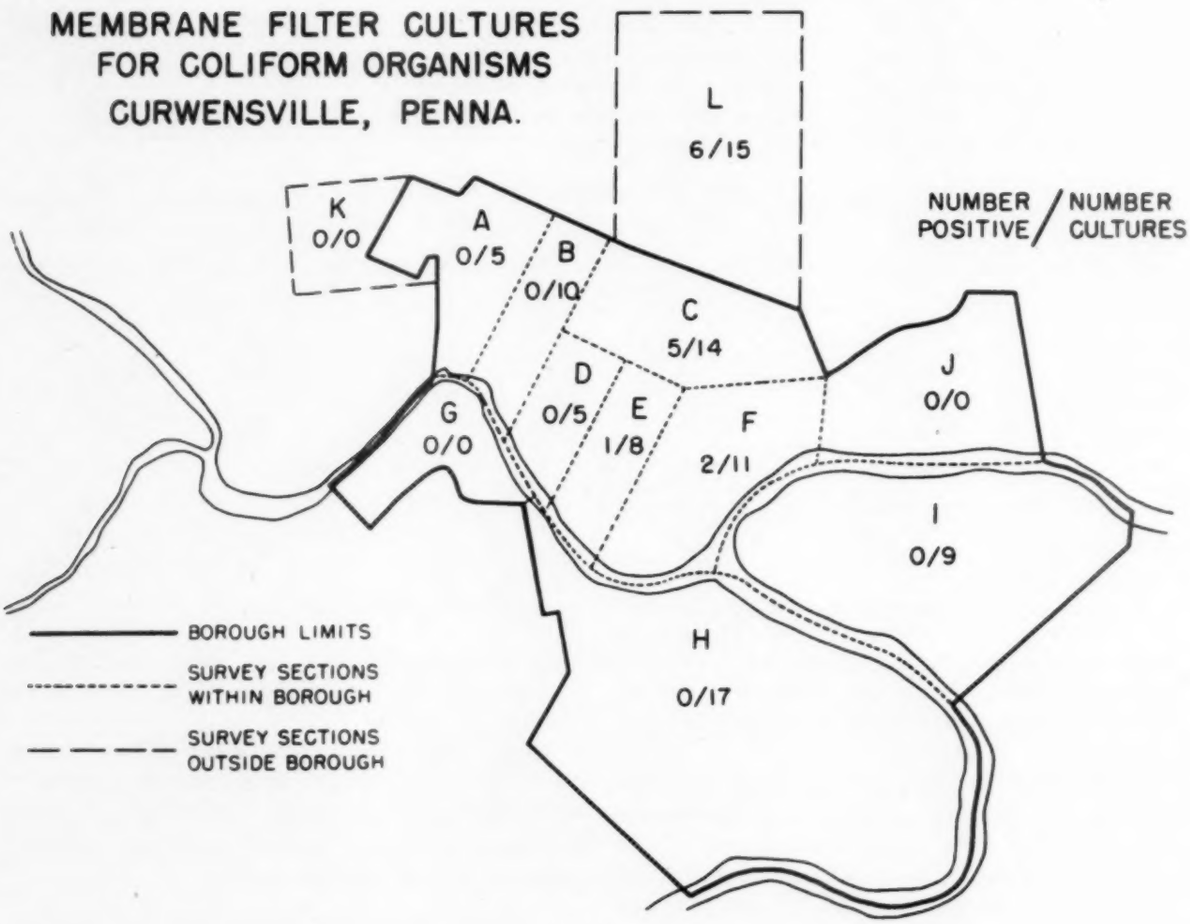

FIG. 4.

carrying the chlorinated supply from the reservoir, so that some mixing probably occurs. The attack rate in sections E and F was 6.7 and 4.2 per cent, respectively.

Sections H and I derive their supply from mains continuing from the junction of the Bailey Spring and main reservoir systems. The rates here were 5.0 per cent and 6.2 per cent, respectively.

Sections A, B, D, G and K derive their water supply largely if not entirely from the reservoir supply. The attack rates in these sections were 0.0, 1.0, 1.4, 1.4, and 1.3 per cent, respectively.

Households in section J derive their water supply entirely from private wells. The only case in this area resulted in a rate of 2.1 per cent.

There were 142 cases among the 3,008 persons served by the municipal water supply, giving an attack rate of 4.7 per cent, while three cases occurred among the 297 persons in these same areas who had a private water supply, a rate of 1.0 per cent. The difference between these groups is significant (p less than 0.01).

School Attack Rates According to Water Supply. Table VIII compares the attack rates in each school among children from homes on the public water supply with those among children from homes not on the public supply. It may be seen that the over-all attack rate in children from homes on the public water supply was 11.6 per cent, as compared with 3.38 per cent in children from homes not on the public water supply attending the same schools. This difference is statistically significant (p less than .001).

The Patton School is located in section B, the Joint School and the South School in section H, and the Locust School in section F. (Fig. 2.) The Joint School, the Locust and the South Schools would receive water from the Bailey Spring system, with the Locust School probably receiving most of its water supply from that main, and the other two schools a part of their

TABLE VIII
ATTACK RATES OF INFECTIOUS HEPATITIS
ALL STUDENTS ATTENDING CURWENSVILLE SCHOOLS
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

School	Grades Included	From Homes on Public Water Supply			From Homes Not on Public Water Supply		
		Students	Cases	Rate per 100	Students	Cases	Rate per 100
Joint School	7th–12th	291	40	13.7	526	15	2.85
Patton School	1st–6th	158	10	6.3	79	1	1.3
Locust School	1st–6th	118	18	15.2	122	10	8.2
South School	1st–4th	82	7	8.5	41	0	....
Total	.....	649	75	11.6	768	26	3.38

supply from it. The Patton School should have received its supply entirely from the reservoir system.

Considering only the Locust and Patton Schools, which derived most if not all of their water supplies from the Bailey Spring and reservoir systems, respectively, and which also had children of the same age group, the attack rates in children from homes not on the public supply was 8.2 per cent and 1.3 per cent, respectively. This difference is significant (p less than .05), and strongly suggests exposure at the Locust School but not at the Patton School, since neither group was exposed to the municipal supply at home. The Joint and South Schools on a mixed supply had intermediate rates among their children.

Table IX gives school attack rates in children from homes on the municipal system according to the probable source of the water supplied. The attack rate in those living in sections probably served entirely by the reservoir supply was 3.0 per cent, which compares with 3.38 per cent in children from homes not on the public supply as seen previously. (Table VIII.) The attack rate among children from homes in the sections served entirely or in part by the Bailey Spring supply was 14.6 per cent. The difference is again statistically significant (p less than .001). This is felt further to substantiate the premise.

CONTAMINATION OF THE MUNICIPAL WATER SUPPLY

Possible Sources. As already noted, there were two unapproved sources of water being used at the time of the epidemic, and these had been in use for a period of at least one to two years. On culture both of these sources were found to be contaminated.

Efforts were made to demonstrate the possible source of contamination with the virus of infectious hepatitis. By reference to Figure 3 it may be seen that one of the two unapproved sources was derived from Hartshorne Run. This stream arises approximately one to two miles above the water intake as a series of small, spring-fed streams. No cases of hepatitis were known to occur in this area during the period December 1955 through February 1956. It was found, however, that three of the houses emptied the overflow from their cesspools into streams contributing to Hartshorne Run. Inquiry at one of the

TABLE IX
ATTACK RATES OF INFECTIOUS HEPATITIS
STUDENTS ATTENDING CURWENSVILLE SCHOOLS WHO LIVED IN HOMES SUPPLIED BY THE MUNICIPAL WATER SYSTEM
EPIDEMIC PERIOD (MARCH 2 THROUGH APRIL 9, 1956)

School	From Sections Probably Served Entirely or in Part by Bailey Spring System			From Sections Probably Served Entirely by Reservoir System		
	Students	Cases	Rate per 100	Students	Cases	Rate per 100
Joint School	217	37	17.0	74	3	4.0
Patton School	72	9	12.5	86	1	1.2
Locust School	111	17	15.3	7	1	...
South School	81	7	8.6	1	0	...
Total	481	70	14.6	168	5	3.0

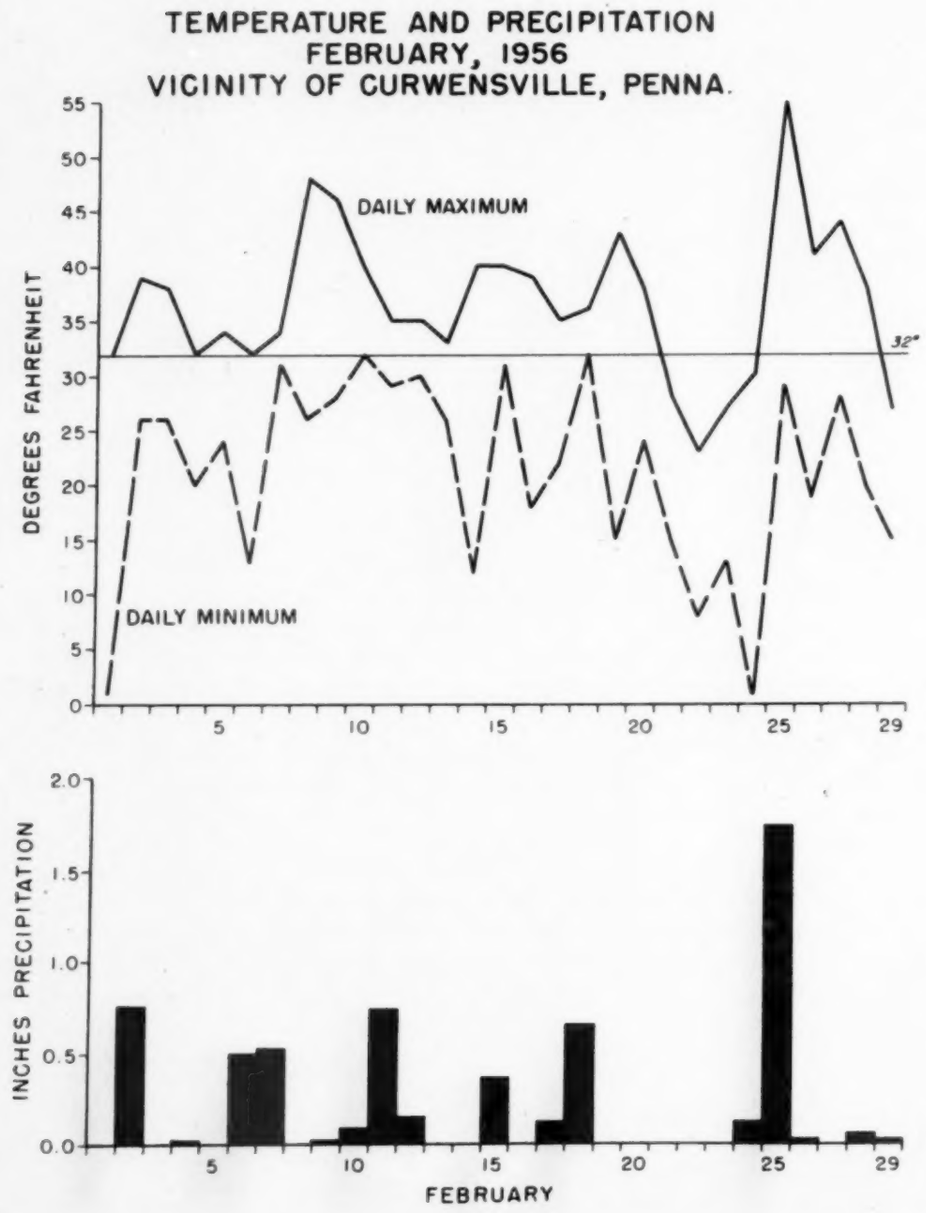

FIG. 5.

houses indicated that there were a number of visitors during the hunting season in December 1955 from the southeast area of the County in which hepatitis had been occurring during 1955. None of these persons became clinically ill but the possibility that one of these was an inapparent case and excreting the virus cannot be excluded.

Sandri Springs was the second source of unapproved water shown to be contaminated. The H. household is located approximately 200 yards from this springs, and two cases are known to have occurred here, one in January and one in February, as mentioned previously when early cases were discussed. This seemed the most probable source. Fluorescein dye tests were carried out from the lateral of the septic tank to determine if dye would appear in the Spring but these attempts were not successful.

It is not possible to say which of these two may have been the source of the virus disseminated in the water supply but it is possible for either to have been.

Possible Time of Contamination. Only two

cases are known to have occurred in visitors to Curwensville. One of these visitors spent every weekend there during this period, and the other was there on February 14 and 15, and again on February 28 and 29.

Typhoid fever epidemics have been found to be related to thawing during winter months with discharge of contaminated material in the run-off. Meteorological data for the area are summarized in Figure 5. Slight thawing accompanied by heavy precipitation occurred during the four-day period, February 25 through 29. The peak of the epidemic curve falls some thirty days later; however, cases began to occur March 2 through March 4, or as early as six days following.

COMMENTS

The time, age and geographic distribution in this epidemic fit only with the hypothesis that one part of the public water supply was a common source vehicle. While this system was interconnected with the other system from the reservoir, and it would have been possible for water from the suspected system to have been distributed to any user, consideration of the probable demand and pressure relationships make it very unlikely that water from the unapproved sources could have reached the west part of the community.

Twenty to forty days is the probable range of the incubation period of infectious hepatitis. If a single exposure occurred the onsets of cases would be expected to fall within a twenty-day period. The thirty-nine days embraced by the epidemic curve is twice this period. This is believed to indicate that contamination was not limited to a few hours, but rather that it occurred over a number of days, probably intermittently. The span of the epidemic curve in the outbreak reported by Tucker et al. [7], in which exposure was probably limited to a single day, was twenty-five days. In the two epidemics reported by Hallgren [8,9] the possibility of continuous or intermittent contamination over weeks or months existed in a population using the water supply daily. The time course of the epidemic in the Hällnäs Sanitorium covered eighty-nine days, with two distinct peaks, and that at the Strömsör Asylum fifty-four days.

Using twenty to forty days as the range of the incubation period infectious material would have had to have been discharged on February 11 to result in an onset as early as on March 2, and as late as March 1, to result in an onset as late as April 9. The cold weather prevailing in the area in February could have permitted intermittent discharge through freezing and thawing. There were several days in early and mid-February when maximum temperatures were in the 40's and minimum were near 32°F. (Fig. 5.) Some contamination could have occurred at these times and more massive contamination on February 25 when warmer weather was combined with 1.62 inches of rain. The peak of the epidemic curve came thirty-one days after the thaw and rain on February 25.

SUMMARY

An epidemic of infectious hepatitis occurred in Curwensville, Clearfield County, Pennsylvania, in March 1956. One hundred twenty-nine cases occurred in Curwensville and an additional forty in the surrounding School Jointure during a thirty-nine-day period. Investigation revealed time, age and geographic characteristics which suggest common source rather than contact transmission. The peculiarities of the municipal water supply fit the epidemiologic data to make this the probable vehicle.

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Review

The Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia*

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"Disease is very old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible." J. M. Charcot

Recent technical advances have added greatly to the ease with which virological methods may be applied to the study of poliomyelitis and allied infections of the central nervous system. These technics have already borne abundant fruit in the development of a vaccine against poliomyelitis. The accurate appraisal of the preventive value of such a vaccine will depend on our ability to diagnose poliomyelitis accurately. It had long been believed that the clinical features of acute paralytic poliomyelitis were sufficiently characteristic for a confident diagnosis to be made on clinical grounds alone. This confidence has recently been shaken by the finding that the virus of louping-ill (Russian spring-summer encephalomyelitis) may produce a similar clinical picture, even in the United Kingdom [*1*]. There is also suggestive but incomplete evidence that Coxsackie B, Echo [*2*] and other viruses [*3*] may occasionally cause acute flaccid paralysis. The position of "non-paralytic" poliomyelitis is even less secure [*4*] and the diagnosis can no longer be established on clinical grounds alone.

The purpose of this article is to review a number of obscure outbreaks of paralytic illness, the majority of which were at first confused with poliomyelitis but which were later differentiated on clinical and epidemiologic grounds. Although investigations have been restricted by the fact that no deaths have occurred, the most careful virologic studies have failed to incriminate the polio virus, the Coxsackie or Echo groups of organisms, or any other known neurotrophic agent. The outbreaks will be compared, and the basis for the view that they constitute a clinical entity will be discussed. Such information as is available about the etiology, prognosis and treatment will be reviewed.

HISTORICAL

In the summer of 1934 an epidemic of poliomyelitis struck Los Angeles [*5*], and many of the sick patients were treated in the Los Angeles County Hospital. Within a few weeks an alarming number of cases of a similar illness had appeared among the hospital staff, particularly in the nurses. As the hospital outbreak developed, certain clinical and epidemiologic features appeared which made the diagnosis of poliomyelitis difficult to sustain. Thus disturbances of sensation and mental symptoms were unduly prominent, and although muscular pain and paresis were the rule, muscular atrophy was a rare sequel. In spite of the fact that no less than

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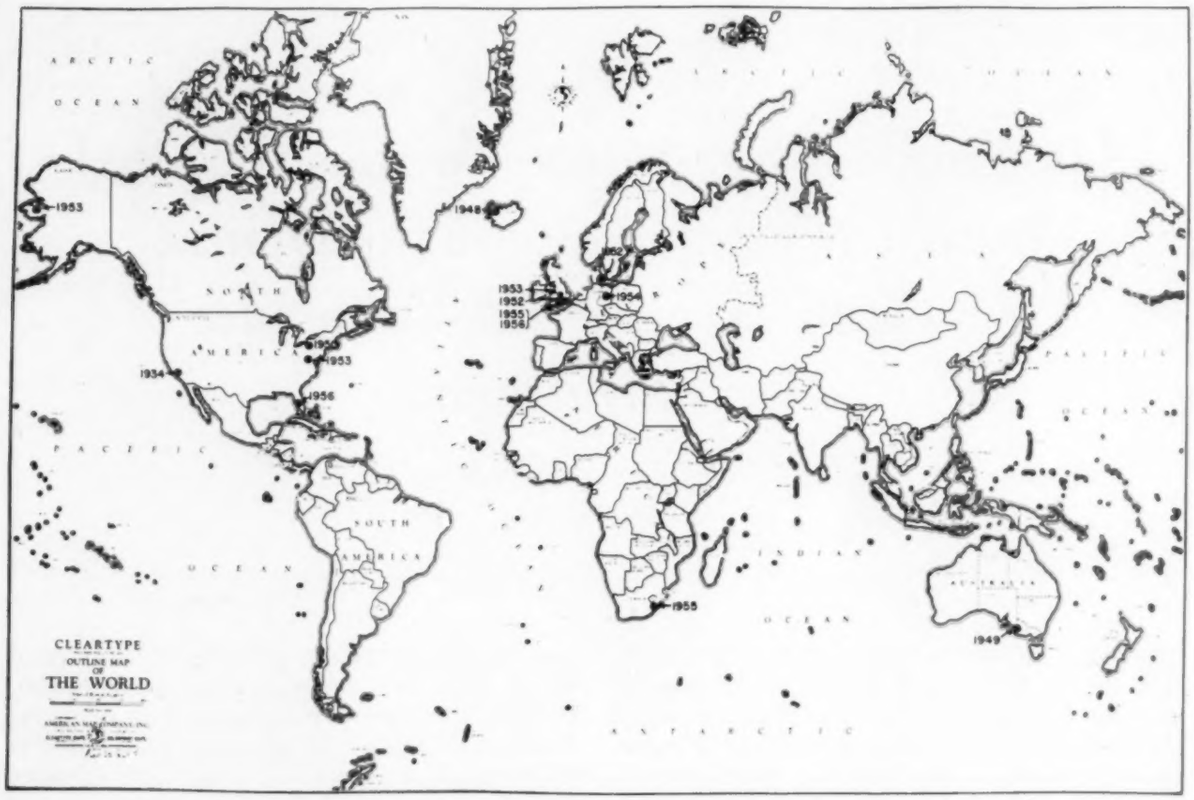

FIG. 1. Geographical distribution of outbreaks.

198 cases developed (an attack rate of 4.4 per cent) there were no deaths, and the general trend of the disease was towards complete recovery. A further distinction from typical poliomyelitis lay in the cerebrospinal fluid, which was normal in fifty-three of fifty-nine cases studied.

After an interval of fourteen years, an epidemic with many features in common was reported in Iceland [*6*], and later other similar outbreaks occurred in Australia [*7*], Europe [*8–13*], the United States [*14–16*], Alaska [*17*], and South Africa [*18–20*]. The names "Iceland disease" (White and Burtch 1954 [*14*]), "Akureyi disease" (Sigurdsson and Gudmundsson 1956 [*21*]), "benign myalgic encephalomyelitis" (Lancet 1956 [*22*]), and "epidemic neuromyasthenia" (Shelokov et al. 1957 [*15,16*]) amongst others have been given to this syndrome. Of the fourteen outbreaks which form the basis of this study, no less than seven have occurred in the staff of hospitals. More than 1,000 persons are known to have been affected up to the present time. The geographical distribution of the outbreaks is shown in Figure 1.

CRITERIA AND DEFINITION

The difficulties in defining a disorder from which no deaths have occurred, and for which no causative infective or toxic agent has been discovered, are obvious. Recognition has to depend on the clinical and epidemiologic pattern. These features must be sufficiently characteristic to separate the disorder from other conditions. A parallel may be helpful. Von Economo [*23*] first described encephalitis lethargica on the basis of the clinical triad of fever, stupor and ophthalmoplegia. Although autopsy material was abundant, the pathologic picture was not in itself distinctive and the findings were often insignificant. No etiologic agent or specific diagnostic test was ever found. It was the clinical pattern and the characteristic sequelae which set the seal on the condition as a nosological entity. Epidemic myalgia (epidemic pleurodynia; Bornholm disease) affords a closer analogy. Here the disease became established as a clinical entity [*24–26*] in spite of the absence of mortality or any specific laboratory test long before the discovery of the Coxsackie group of viruses.

In the instance under discussion, the problem has been attacked by making a clinical and epidemiologic analysis of a number of similar outbreaks in which it has been difficult to sustain a diagnosis of poliomyelitis or any other known infection of the nervous system. All the outbreaks shared the following characteristics: (1) headache; (2) myalgia; (3) paresis; (4) symptoms or signs other than paresis suggestive of damage to the brain, spinal cord or peripheral nerves; (5) mental symptoms; (6) low or absent fever in most cases; (7) no mortality. In addition, (1) a higher frequency in women; (2) a predominantly normal cerebrospinal fluid, and (3) relapses have occurred in almost all outbreaks. In eleven of the fourteen epidemics symptoms which suggest activity of the disease have persisted for months or years in a few cases, and in eight instances there was an apparent predilection for the nursing or medical professions. Lymphadenopathy was a feature in four outbreaks.

The case for an entity will depend on the distinctiveness of these findings.

EPIDEMIOLOGIC FEATURES

Of the fourteen outbreaks considered in this paper, seven occurred amongst the staff of hospitals; one in an army barracks; two in small towns; two in semi-rural communities, and two in the populations of large cities. The attack rate was measured in eight outbreaks. It varied from 2 per cent* in the Middlesex Hospital Nurses' Home [*8*] to approximately 20 per cent* in the Nurses Homes at Durban [*18*] and Coventry [*10*]. At the Los Angeles County Hospital [*5*] the attack rate was 19.0 per cent among nurses, and 4.4 per cent for all employees, resident or living out. At the Royal Free Hospital in London [*27*] the figures were 18.3 per cent for nurses and 8.3 per cent for the whole population at risk. In the small communities at Akureyri in Iceland [*6*], Seward in Alaska [*17*] and Punta Gorda in Florida [*16*], the attack rates were approximately 6 per cent. These attack rates were much higher than usually seen in poliomyelitis.

Ten of the twelve outbreaks in the Northern Hemisphere commenced between April and September. The exceptions were the epidemic in Punta Gorda [*16*] which commenced in February and the small outbreak in Berlin [*11*] which began in November. In the Southern Hemisphere the outbreaks began in February (Durban) [*19*] and August (Adelaide) [*7*].

On the basis of case to case contact, attempts have been made to fix the incubation period of the disorder. In the Iceland [*6*], Bethesda [*15*], Royal Free Hospital [*27*] and Punta Gorda [*16*] outbreaks the evidence indicated an incubation period of less than one week, probably five to six days. In Los Angeles [*5*] the information on this point is incomplete, but a few patients became ill four days after their first exposure, indicating the minimum incubation period. On the other hand, the Middlesex Hospital [*8*] and Durban [*18*] reports suggested a longer period of two to three weeks. An incubation period of fourteen days was present in the single case in which isolated contact occurred in the small second outbreak in the Royal Free Hospital in 1956 [*13*].

The general consensus is that the disorder occurs more frequently in women. (Table 1.) This is certainly true of the outbreaks in hospital staffs. In the Middlesex [*8*], Coventry [*10*] and Durban Hospitals [*18*] no men were affected, and only one man became ill at Bethesda [*15*]. In the Los Angeles [*5*] and Royal Free Hospital [*27*] outbreaks the attack rates for women were 6.4 per cent and 10.4 per cent respectively, and for men 1.6 per cent and 2.8 per cent. The higher attack rate in women on the staff of a hospital might indicate an occupational hazard rather than a true sex susceptibility. However, outbreaks in the general population confirm the higher incidence in women noted in the hospital cases. White and Burtch [*14*] regarded the ratio of 15:1 in favor of women in their small series as due to chance. Poskanzer and his colleagues [*16*] believed that in Punta Gorda, women were affected both more commonly and more severely than men. If the figures for white people and Negroes derived from their house to house survey are combined, the attack rate for women is 8.2 per cent, and for men 4.0 per cent. This female predominance is largely due to a high incidence in Negro women. Sigurdsson [*6*] found that at Akureyri females were affected more commonly than males in the ratio of 8:5. All patients studied by Fog [*9*] in Copenhagen were female. In the Alaska [*17*] outbreak, the syndrome developed in 122 females and 53 males. The attack rates in these two outbreaks cannot be calculated as the population by sexes is not given. Sporadic cases [*28–32*] are also

* The denominator is the total number of nurses employed.

TABLE 1
ATTACK RATES BY SEX

Outbreak	Males			Females		
	Population at Risk	No. of Cases	Attack Rate per 100	Population at Risk	No. of Cases	Attack Rate per 100
Los Angeles 1934	1,779	28	1.6	2,536	168	6.4
Iceland 1948–49	3,339	171	5.1	3,548	294	8.3
Royal Free Hospital 1955	950	27	2.8	2,550	265	10.4
Punta Gorda 1956	497	20	4.0	513	42	8.4

reported more frequently in women than in men. The single outbreak with a predominance of affected males was that described in a military barracks in Berlin [*11*]. The patients were all men.

All age groups have been affected from late childhood [*6,14,16,17*] to the eighth decade [*16*]. However, many reports stress the high frequency among young adults. In the Los Angeles outbreak [*5*] the figures show a striking selectivity of the disorder for women between the ages of twenty and twenty-nine. In men the relationship to age was irregular. In the Middlesex Hospital [*8*], Coventry [*10*], Durban [*18*], Bethesda [*15*] and Berlin [*11*] outbreaks most of the cases occurred in the third decade, but this may be due, in part at least to the composition of the population at risk. Figures from which attack rates may be calculated by age are not given. In the Royal Free Hospital outbreaks [*12,13*] the incidence was higher in the nineteen to thirty-five age group (11 per cent)* than in older people (4 per cent).* In Iceland [*6*] the highest incidence was in adolescents aged fifteen to nineteen. Cases in small children have been rare.

A prevalence of poliomyelitis in the area of the outbreak has been noted on several occasions and has made differential diagnosis difficult. The most striking example is the Los Angeles outbreak [*5*] of 1934. There the cases among the staff occurred after the admission of large numbers of patients with poliomyelitis from the city and the rise and fall of the epidemic in the city corresponded closely with that of the hospital outbreak. Virus studies and autopsy material proved that the city epidemic was poliomyelitis, although there were certain atypical features [*5*].

* Approximate figures.

However, the clinical characteristics in the cases among the staff differed in important particulars. Coincident outbreaks of poliomyelitis also occurred in Copenhagen [*9*], New York State [*14*] and Alaska [*17*]. In Adelaide [*7*] and Durban [*18*], epidemics of poliomyelitis preceded the outbreaks of illness and in Iceland [*6*] there were a few cases of typical poliomyelitis at the beginning of the outbreak. At Coventry the outbreak occurred amongst the staff of an infectious diseases hospital which was commonly concerned with the treatment of poliomyelitis. In the Middlesex [*8*], Bethesda [*15*], Royal Free Hospital [*12*], Berlin [*11*] and Punta Gorda [*16*] outbreaks there was no known association with poliomyelitis.

Most curious of all the epidemiologic features is the apparent susceptibility of the nursing, medical and ancillary professions. Seven of the fourteen outbreaks have occurred in the staffs of hospitals. In one other [*16*] a high attack rate among nurses, doctors and their helpers was noted. Thus the attack rate among medical personnel was 40 per cent (sixteen of thirty-eight) as opposed to 6.1 per cent (62 of 1,010) in the community as a whole. In the Los Angeles [*5*] and Royal Free Hospital [*12*] outbreaks the attack rates were higher in nurses than in the other hospital staff. In the Middlesex [*8*], Coventry [*10*], Bethesda [*15*] and Durban [*18*] epidemics the disorder was virtually confined to nurses.

It is recognized that nurses through contact with patients have an increased risk of contracting certain infections. As far as this syndrome is concerned, however, there has been evidence that the nurses might have been infected by patients in only two outbreaks [*5,10*]. Thus, in Los Angeles [*5*], cases occurred both earlier and

more commonly in those members of the hospital staff who were in close contact with patients with poliomyelitis who had been admitted from the city. On the other hand, the clinical evidence suggests that the illness among the staff was different. In the Coventry Hospital [*10*], the disorder may have reached the staff by way of the patients. Galpine and Brady [*32*] were of the opinion that some of the cases admitted immediately prior to the outbreak in the staff in Coventry were not poliomyelitis but an illness identical with that which affected the staff. In the remaining five institutional outbreaks there is no evidence that nurses were infected by patients. Spread in the reverse direction (nurses *to* patients) has either been extremely uncommon [*12,15*] or absent.

This apparent predeliction for medical personnel, particularly nurses, remains one of the most difficult and interesting features of these outbreaks. It should be recalled, however, that a high standard of diagnostic skill is usually available to nurses, and that similar outbreaks in other types of residential institutions may have been unrecorded.

Observations concerning the possible mode of spread are available in nine outbreaks. In eight there is good reason to suppose that the agent responsible was not food- or water-borne. The distribution of cases did not correspond with any source of water or food. In the Iceland outbreak spread occurred along the main traffic route from Akureyri. Instances of spread by personal contact have been recorded [*8,13,27*] and most authors agree that this is the probable means of dissemination. The best authenticated example is cited by Crowley [*27*]. A nurse who had attended the first and fourth girls to fall sick in the Royal Free Hospital epidemic became ill six days later. During the incubation period "she had accompanied a surgical case from ward to operating theatre, remained in attendance during the operation, and escorted the case to bed in a different ward. The patient, the ward sister, the theatre sister, a medical officer, a medical student working in the theatre, and the second ward sister all became ill within eight days." In the Bethesda outbreak [*15*] the discovery of a paracolon organism in the stools of a large proportion of the affected nurses and in a kitchen attendant focussed attention on the possibility of food-borne infection. However, only one doubtful case developed among the patients who were also supplied with food from the same source. The world-wide distribution of the outbreaks (Fig. 1) together with the marked differences in the types of community affected are points against either an insect vector or a toxic agent, both of which have been sought without success.

CLINICAL FEATURES

An exact numerical comparison of the symptoms and signs reported in the various outbreaks is not possible. Thus in some instances only cases selected on the basis of severity or convenience were examined in detail [*6,9,14,16*] while in others [*5,8,12*] in over-all picture of the outbreak was provided. Reports of the Durban epidemic are fragmentary, and it has been necessary to refer to unpublished data [*18*]. The description of the Adelaide epidemic [*7*] differs from the rest of the material in that it refers only to cases which were admitted to an isolation hospital from an urban community. Presumably, this would bias the material in favor of severe cases.

Broadly speaking, the epidemic cases have fallen into two groups: patients with definite localized muscular paresis, and those without. Only the former will be described in detail, as it is doubtful whether the latter could be distinguished from many other illnesses in the absence of an epidemic. The frequency of paretic cases in the various outbreaks has varied from about 10 per cent in the Punta Gorda outbreak to 80 per cent in Los Angeles. An approximate over-all figure is 40 per cent.

Mode of Onset. The onset of the illness has usually been abrupt. According to Gilliam's detailed report [*5*] the onset in the Los Angeles cases was sudden, the most prominent early symptoms being headache and muscular pain, both of which occurred in over two-thirds of all cases during the first three days of the illness. Next in frequency were nausea, which occurred in about half the cases, and sensory disturbances, stiffness of the neck and back in about one-third. Fever, with a temperature in excess of 100°F., was found in only a quarter of all cases and in almost all of these it appeared on the first day of the illness. Muscular tenderness and localized pareses were uncommon initial symptoms, but by the end of the first week they had developed in about half the cases.

In the Akureyri outbreak [*6*] pains in the neck and back were almost universal in the first few days of the disease. Low fever was also

common. Within a few days pains accompanied by paresthesias appeared in the limbs. In the more severe cases fibrillary twitchings of muscles were also noted. In the paralytic cases paresis usually appeared three to seven days after the onset.

According to White and Burtch [*14*] the onset of illness in the Thousand Islands district of New York State was acute in four and insidious in fifteen of the cases selected for detailed study. The average duration of symptoms prior to the initial examination was twenty-one days. In retrospect, the commonest presenting symptoms were found to have been muscle pain and headache associated with low fever. Coryza, sore throat, cough, nausea and diarrhea were also noted during the first few days. An exact account of the time of onset of paresis was not given, but it seemed likely from the two "representative case reports" that it did not occur before the end of the first week.

In the Adelaide epidemic [*7*] the onset was abrupt with stiff neck and backache. Headache, pain on moving the eyes, malaise, aching in the limbs and hyperpathia were other common early symptoms. It should be recalled, however, that only patients sufficiently ill to be admitted to an isolation hospital from a city were dealt with in this report, a striking contrast to the selection of the New York cases.

In the Middlesex Hospital outbreak [*8*], like the other epidemics involving hospital staffs, the whole population at risk was under close medical supervision throughout. In most cases symptoms appeared abruptly. Headache, malaise and backache were almost invariable, and pain in the limbs occurred early in ten of fourteen cases. Mild pyrexia was present at the onset in nine cases. Vomiting and diarrhea occurred infrequently. In one case there was a definite biphasic illness similar to that which is seen in poliomyelitis.

According to Fog [*9*] headache associated with low fever was an invariable initial symptom in the Copenhagen patients. In a few it was accompanied by stiffness of the neck or back, nausea, vomiting, dizziness and pain in the limbs.

In the Coventry epidemic [*10*] the preparetic symptoms were usually insidious and insufficiently severe to make the patients report sick before the onset of paralysis. The premonitory symptoms included sore throat, headache, backache, nausea, chills and lethargy. Paresis developed from two to thirteen days after the onset of these symptoms, usually on the sixth day. In only six of the thirteen patients was fever noted after reporting sick, and in none of these did it exceed 100°F.

In their description of the Bethesda outbreak, which occurred in the staff of a psychiatric hospital, Shelokov and his colleagues [*15*] confined their detailed description to the twenty-six confirmed paretic cases. Twenty-one of these patients presented with premonitory symptoms before the onset of paralysis. The prodromal illness was characterized by malaise, headache, aches and low grade fever, which lasted from four to six days. Sometimes there was an interval of apparent well-being between the prodromal illness and the paretic manifestations. Occasionally, the prodromal illness was prolonged by the appearance either of acute respiratory or gastrointestinal symptoms, namely, cough, diarrhea, nausea and vomiting.

In the small outbreak in an army barracks in Berlin [*11*] the patients presented with abrupt onset of headache and low fever. Three days later muscular pains, backache and photophobia appeared.

According to Adnams [*18*] most of the patients amongst the staff of the Durban Hospital became ill with severe occipital headache, stiffness of the neck, backache and weakness of the muscles of the back and abdomen. Heaviness, weakness and paresthesias in a limb or limbs followed within twenty-four hours. Prodromal symptoms of lassitude, sore throat, vomiting and diarrhea in the preceding ten to fourteen days were sometimes volunteered by the patient, but more frequently were ascertained only by direct questioning. It would appear, therefore, that the prodromal illness in this outbreak was mild in most cases. According to Hill [*19*] coryza and sore eyes were also occasional prodromal features.

Both in size and in the wealth of clinical detail reported, the Royal Free Hospital epidemic [*12*] compares with the Los Angeles outbreak of 1934. The following presenting symptoms occurred in at least a third of the 200 patients in whom records were complete. In order of frequency they were headache, sore throat, malaise, lassitude, vertigo, pain in the limbs and nausea. A striking feature was the intensity of the malaise, which was out of proportion to the slight pyrexia. In only nine cases (4.5 per cent) was a temperature over 100°F.

recorded. On examination the superficial lymph nodes of the neck were enlarged in almost every case, particularly in the posterior triangle. Paralysis and other neurological signs developed toward the end of the first week in many cases. The small second outbreak affecting the Preliminary Training School of the same hospital a year later [*13*] had a similar pattern of onset.

According to Poskanzer and his colleagues [*16*] the onset of the Punta Gorda outbreak was insidious, and was marked by fatigue, headache, pains in the back and limbs, depression and instability. The average period between onset and confinement to bed was nineteen days with a range of one to sixty-five days. In half the patients there was a sudden exacerbation of symptoms one to four weeks after the onset.

The Fully Developed Acute Illness. Gilliam's [*5*] account of the Los Angeles outbreak is of particular interest, not only because of the richness of the clinical detail but because it is the first definitive description of the illness in the literature. The postwar European, Icelandic, Adelaide and Durban epidemics were recorded without knowledge of Gilliam's findings and are unbiased by his interpretation of them. The Los Angeles outbreak therefore affords an ideal basis for comparison with later epidemics.

Severe generalized headache was almost invariable (94 per cent) and was accompanied by some stiffness of the neck or back in two-thirds of the patients. Pain in muscles was also an almost constant feature. The common sites were the neck, shoulders and limbs. It varied in intensity, both from case to case and from day to day, and was usually aggravated by exertion. In severe cases it was agonizing and unresponsive even to opiates. When severe, it was accompanied by exquisite muscular tenderness, tender nerve trunks and by skin sensitivity so that the affected limb required cradles to prevent contact with bed clothes. Muscular twitching, sometimes sufficient to move a whole extremity, was noted and cramps were frequent. Definite paresthesias occurred in 42 per cent of the cases. Low fever, with temperatures which uncommonly rose above 100°F., accompanied these symptoms during the first few days.

Localized muscular weakness developed in 80 per cent of the cases. It was notably variable both in site and in intensity from day to day. Of a total of 152 paretic cases, the weakness was noted within the first fourteen days in 119. In about half it had cleared within four weeks, and in a further 25 per cent within eight weeks. In 12 per cent demonstrable paresis was present three months after the onset.

There is a notable absence of information about the changes in tone, sensation and deep reflexes associated with the paresis. Gilliam admits that full neurological examinations were rarely performed; this was doubtless due partly to the pressure of the epidemic. More important perhaps is the fact that orthopedic surgeons rather than internists had much of the clinical responsibility. As it was, patchy anesthesia was noted in a few cases, diplopia in thirty-one, facial paresis in three and difficulty in swallowing in six. Other cranial nerve symptoms or signs were found in eleven patients. True vertigo was rare and hyperacusis and deafness were not recorded. Two patients required treatment in a respirator for a short time.

Urinary retention requiring catheterization was a complicating feature in 12 per cent. It was frequently accompanied by constipation. Although these symptoms developed only in the paralytic cases following total immobilization in Bradford frames, Gilliam was satisfied that the time relationships showed that they were a real part of the illness and not an artifact introduced by the mode of treatment.

Gilliam observed the mental symptoms which have been an almost constant feature of more recent outbreaks. Later writers have also shared his perplexity in assessing their significance. In the Los Angeles outbreak they occurred in 30 per cent of the patients. His original description of them deserves direct quotation. "The emotional upsets reported are difficult to interpret. They varied in degree from relatively slight displays of irritability and impatience to violent manifestations of dislike for people and things formerly liked. A common type of upset consisted of crying spells resulting from no known provocation. The emotional upsets of a few individuals were undoubtedly hysterical in nature, but it would be manifestly erroneous to consider as hysteria the emotional instability associated with this illness in all of the cases in which it was present. Other disturbances chiefly consisted of loss of memory and difficulty in concentration. Transient personality changes of varying degrees of severity were relatively common." Coma and reversal of sleep rhythm did not occur. After running a course of four to eight weeks, the illness abated and paresis disappeared in most cases. However, in some cases one or

more well defined relapses occurred. The average period of hospitalization was eight weeks.

In the Iceland outbreak [*6*] paresis was usually confined to a single muscle group, the abductors of the shoulders and the abductors and rotators of the hip being the most commonly affected. Paresis was accompanied by an exacerbation of pain and tenderness in the muscles concerned, together with paresthesias. In severe cases, hyperpathia or anesthesia developed in the affected limb. Coarse muscular twitching was common, but true fasciculation was absent. The paralysed limb was always hypotonic, although reflex changes were reported as variable. Extensor plantar responses were not noted. Cranial nerve palsies were rare and urinary retention was reported in two cases only. Emotional lability, irritability, depression and lack of concentration appeared in convalescence and were extremely troublesome. The duration of the illness in the milder cases was from two to four weeks and in the more severe cases from two to three months.

In the New York State cases [*14*], muscular aching often accompanied by head or neck ache was the most consistent symptom. It affected the muscles of the shoulder girdle in seventeen of nineteen cases at some state of the illness, but other muscles were usually involved and pleuritic chest pain was also reported. The aching was invariably accompanied by muscular tenderness and usually by hyperpathia and paresthesias. Muscular weakness, which was common, never coincided with the distribution of the tenderness. The deep tendon reflexes were usually reduced in the weak limb, but atrophy did not develop. Sensory loss was noted in three cases. Marked mental depression occurred in eleven of the nineteen subjects studied.

In the Adelaide outbreak [*7*] the acute illness was short. Following the development of severe headache and mild generalized muscular aching, widespread paresis occurred. It cleared rapidly after a few days. Cranial nerve palsies, paresthesias and hyperpathia were rare. Retention of urine occurred in a number of cases. A recrudescence of the disease, characterized by hyperacusis, depression and fatigue, often occurred four to eight weeks after the original illness. It was protracted and resistant to treatment.

In the Middlesex Hospital outbreak [*8*] the characteristic features were "the association of severe muscular pain affecting the back, limbs, abdomen and chest with evidence of mild involvement of the central nervous system in which the weight of the damage appeared to fall on the pyramidal tracts, the posterior columns, and the cranial nerves rather than on the anterior horn cells." Following the prodromal symptoms already described, nine of the fourteen patients experienced sudden onset of pain, tenderness spasm and paresis in the muscles of a limb or limbs associated with paresthesias and hyperpathia. The discomfort was always sufficiently severe to require full doses of analgesics for relief. Any handling of the limb at the bedside was resented and the patient could not bear the weight of the bed clothes upon it. The paresis was usually most marked in the distal muscles and was accompanied by variable reflex changes. The plantar response was frequently extensor on the paralysed side and loss of vibration sense was common in affected limbs. Pleuritic chest pain and urinary retention and incontinence were also prominent features. In the cranial nerves nystagmus was almost invariable, and vertigo, deafness and paresis of the soft palate were also reported. One patient was nursed in a respirator for a short time. In most cases the muscular pain and paresis had disappeared by the end of the third week. Relapses in the second and third weeks occurred in a few cases. Emotional disturbances were common in the acute stage, but did not persist into convalescence [*8a*].

In Copenhagen [*9*] the fully developed syndrome was characterized by severe pain and unpleasant paresthesias in the extremities. Definite paresis associated with increased deep reflexes was present in one patient and weakness and clumsiness in several others. Hyperhidrosis and muscular tenderness also occurred in the affected limbs. Nystagmus, diplopia, ptosis and extensor responses were each noted on one occasion. Depression and mental lability were prominent.

In the Coventry cases [*10*] the onset of paresis was coupled with an exacerbation of headache and pain in the neck and usually first manifested itself by clumsiness and heaviness of a limb. Muscular pain occurred but does not appear to have been severe. Chest and abdominal pain are not described. Tenderness, unsteadiness in response to effort and hyperpathia were often noted. Temporary loss of position sense was found in four patients. The deep reflexes in the affected limb were usually diminished and the plantar responses were flexor. Difficulty in

micturition was noted in four cases. Recovery took place in some instances within a month, and in all cases was substantially complete within two months. Lack of concentration and ability to memorize was described as a characteristic symptom in convalescence.

Shelokov's [*15*] description of the Bethesda outbreak resembles the Coventry epidemic in many ways. The onset of paresis was heralded by an exacerbation of the headache and stiffness of the neck, together with heaviness and numbness in one or more limbs. Myalgia and muscular tenderness were invariable in the paralysed limbs and pleuritic chest pain was also noted. Paresthesias were common and were sometimes accompanied by changes on formal sensory testing. Nervousness, unprovoked crying spells, difficulty in concentration, undue irritability and anxiety occurred in nineteen of twenty-six patients studied in detail. Nausea, diarrhea, somnolence and insomnia were unusual manifestations of this outbreak. Cranial nerve palsies were not mentioned.

In the Alaska outbreak [*17*] muscular pain was accompanied by photophobia, hyperacusis, disturbances of taste and extreme anxiety. Paresthesias were common. Use of the affected muscles exacerbated the pain, but marked muscular tenderness did not occur. Tremors in the acute stage were a bad prognostic sign as far as the subsequent development of paralysis was concerned. Muscular weakness was widespread and commonly affected one or the other side of the body exclusively. Incoordination and myoclonic jerks were also seen, and constipation and transient urinary retention were common.

The clinical account of the small Berlin outbreak [*11*] is incomplete. Severe pains in the limbs with muscular tenderness were invariable. Paresthesias and other sensory changes are not mentioned. Slight muscular weakness unaccompanied by reflex changes developed in three of the seven cases and hyperacusis in two. Depression was a feature in three patients and persisted into convalescence. Conjunctival injection occurred in five patients and an erythematous rash in two.

In the extensive outbreak among the nurses at the Addington Hospital, Durban [*18–20*] the onset of paresis, backache, shoulder girdle and subcostal pain followed an ill-defined period of prodromal symptoms. Headache, if pre-existing, became very severe at this stage. Weakness of the abdomen and back were so common that the inability to sit up from the supine posture became an important early diagnostic sign. Paresis in a limb was usually accompanied by paresthesias and patchy sensory loss. Posterior column signs were also noted. The deep reflexes were usually altered in a paralysed limb. Although the plantar responses were equivocal on a number of occasions, they were never frankly extensor. Retention of urine occurred in ten cases. Affection of the cranial nerves was rare [*19*] and was limited to a few instances of facial paresis and perceptive deafness. Mental symptoms were prominent, particularly in the severer cases and included defective concentration and memory, drowsiness, emotional instability and nightmares. In the majority, full recovery occurred within two months. Muscular atrophy was never observed.

In the epidemic at the Royal Free Hospital [*12*] no clear division of symptoms into those appearing early and late was possible. Neurological manifestations appeared most commonly in the second and subsequent weeks of the disease, but occasionally in the first. The fully developed clinical picture consisted of pain in the neck, back, subcostal region or limbs, out of all proportion to the degree of pyrexia, and general constitutional disturbance, and dizziness. The intensity of the symptoms fluctuated widely from day to day but on occasion the pain required the strongest analgesics for relief. Pyrexia rarely reached 100°F., and there was little tachycardia. Tender enlargement of the cervical lymph nodes was almost invariable. The liver was palpable in 8.5 per cent of cases.

The neurological symptoms and signs which developed in 148 cases (74 per cent) were believed to form "a characteristic picture that distinguishes this disease from other infections of the nervous system." Hypersomnia, nightmares, panic states, uncontrollable weeping and amnesia were frequent symptoms in the acute state. In six patients severe mental illness developed in which the dominant feature was depression. Two of these had to be committed and subsequently were treated with convulsive therapy; a third took her own life. Cranial nerve lesions occurred in sixty-nine of the 200 fully documented cases, the ocular, facial and acoustic nerves being most commonly affected. Bulbar palsy appeared in eleven cases.

In the limbs, motor weakness occurred in 102 patients and sensory disturbances in eighty-two. The paresis was almost invariably accompanied

by pain and marked muscular tenderness and the slightest attempt at active or passive movement was resented. Cutaneous hyperpathia, paresthesias and loss of position and vibration sense were common accompaniments. Spasm, fasciculation and myoclonic jerks occurred less frequently. The paresis was usually most marked in the peripheral muscles and was commonly of hemiplegic distribution. The deep tendon reflexes were sluggish in the early stages and exaggerated later in the disease. They were never abolished. Frank extensor plantar responses occurred in two cases only, but equivocal or absent responses were common. Muscular wasting occurred in two cases. Bladder dysfunction, including retention of urine, developed in one-fourth of the patients. In the phase of recovery, jerkiness of the paretic limbs in response to voluntary movement was noted and considered to be characteristic. (A similar phenomenon was also noted in the Coventry and Durban outbreaks.)

The clinical picture of the Punta Gorda outbreak [*16*] was described on the basis of the findings in twenty-one of thirty patients interviewed between May 24 and June 6, 1956, "who presented similar histories of illness, and had no major intercurrent medical problems." It will be recalled that these patients had been ill with vague symptoms for periods ranging from one to sixty-five days. The most prominent general symptom was fatigue coupled with headache, pain in the neck, nausea and vomiting. Depression and impaired memory was present in nineteen, and was associated with terrifying dreams and episodes of crying without provocation. Symptoms suggesting involvement of the central nervous system consisted of paresthesias, unsteadiness, vertigo, blurring of vision and diplopia. The account of paresis is confusing and is recorded as present in eight cases in the text, and in only two cases in the accompanying table. In any case, it appears to have been mild and localized, and other neurological signs were absent. It seems that the illness in Punta Gorda ran a subacute rather than an acute course, and that objective evidence of disease was minimal.

Status of Patients on Discharge from Hospital. In addition to formal follow-up studies, some information is available about the state of health of the patients on discharge from the hospital, and in the case of nurses, about the total time lost from work.

According to Gilliam [*5*], the average period which elapsed from the onset of illness to return to duty in Los Angeles was 13.6 weeks, but this figure is based on less than half the cases, as 55 per cent of the patients were still on the sick list at the time of his report. When he last observed them, forty-three patients (22 per cent) still had definite localized paresis, and in eighteen this was moderate or severe. Muscular atrophy was a rare sequel and in the ten cases in which it was noted it was slight. He stated that the irregularities in the course of the disease and the peculiarities of the paresis forbade an accurate estimate of the recovery rate.

Adnams [*18*] gives an account of the disability rate in the Durban Hospital outbreak six months after the appearance of the last case. Of ninety-eight nurses, fifty had returned to full duty with no apparent sequelae, and a further thirty-two were on duty with "mild or more serious residua." Seven were on sick leave with serious sequelae, seven were on vacation or had resigned, and two had been readmitted to the hospital in relapse. In mild cases full recovery of muscular power occurred within a few days and convalescence, which was punctuated by headache, aching and fatigue, was complete within a month. In moderate cases the return to normal took three to four months. In the severe cases, which fortunately were few, relapses were continuing up to seven months after the onset.

In the Royal Free Hospital outbreak [*12*], the duration of hospital in-patient treatment was less than one month in 57 per cent; from one to two months in 28.5 per cent; from two to three months in 7.5 per cent and more than three months in the remaining 7 per cent. Convalescence was very prolonged, "and extreme fatigue and general aches and pains made the rehabilitation period extremely tedious and long." A period of six weeks convalescence was found necessary for patients who had been in bed for more than a month. Even when this was completed many patients could work only four hours a day. Four patients still had marked disability at the time of the report, two years after the epidemic. In one patient choreoathetoid movements had developed in her paralysed right hand; two required leg callipers and a fourth crutches.

In the Middlesex Hospital outbreak [*8*], seven of the fourteen patients showed no physical signs of disease on discharge from the hospital on an average of one month after the onset. Of

the remainder, four showed mild pyramidal tract involvement, one had absent position and vibration sense in the right foot, another had mild bilateral deafness of the inner ear, and a third had patchy anesthesia involving the left thigh with marked tenderness of the underlying muscles.

The Aftermath. Relapses: The majority of patients afflicted in these outbreaks have been discharged from the hospital within two months and have returned to work after a period of convalescence prolonged by fatigue, aches and pains, depression and lack of concentration. However, in a proportion which has varied from outbreak to outbreak, relapses or a chronic state of ill health have developed.

Relapses have been a feature of all outbreaks except one (Coventry [*10*]). They have usually occurred within a week or two of the initial illness, while the patient was still in the hospital, but in some instances they have necessitated a second admission to the hospital. In the New York State cases [*14*] the timing of the relapses was not described, but they are mentioned indirectly as a feature in common with the Iceland outbreak. In the Punta Gorda outbreak the course was subacute from the onset and exacerbations, rather than relapses, occurred. In five outbreaks [*5,9,15,16,17*] relapses or exacerbations of symptoms in women have coincided with menstrual periods. Physical exertion and cold weather have also been incriminated. Most reports indicate that the chance of relapse diminished with the interval after recovery from the initial illness and that recurrences are rare after the end of the third month. However, Deisher [*17*] described cyclical recurrences in many of his patients up to two and a half years after the first illness, but it is not clear whether these were relapses in apparently healthy people or repeated exacerbations of chronic symptoms. Galpine and Brady [*32*] have described a second attack three years after a previous similar illness. There had been complete recovery in the interim with perfect health.

The relapses have consisted either of a return of paresis to areas previously affected, or to fresh areas, accompanied in some cases by fresh neurological signs, or simply of fresh muscular pains or mental symptoms. Fever is a frequent but not invariable accompaniment. Little has been added to Gilliam's original description, "Following a recrudescence of constitutional symptoms there was frequently an extension of pain or weakness into muscle groups not previously involved. In many cases the constitutional symptoms during the recurrences were considerably more severe than at onset. . . . The milder "relapses" were sufficiently annoying that all convalescents were constantly "keyed up" in fear they would develop one. There appeared to be no predisposing cause for them, though in many, they were associated with untimely overexertion or with some phase, usually the onset, of menstruation. Cold damp weather frequently increased pain and a sense of ill-being in patients in whom a definite recrudescence was not precipitated. A few of the "relapses" were unquestionably hysterical in nature." It is interesting to compare the description of relapses in the Royal Free Hospital outbreak, which was written without knowledge of Gilliam's account. "There might be periods of two weeks in which the symptoms were mild and fever had disappeared. Such periods were often followed by marked recrudescence of old symptoms and sometimes by the appearance of fresh neurological manifestations. In such relapses further fever and tender enlargement of glands occurred. Relapses occurred in some cases after patients had been fit enough to return to their homes. . . . Functional manifestations in a few cases overlaid the organic picture, particularly in those cases longest in hospital."

The subacute and chronic stages: In seven of the recorded outbreaks, a proportion of the patients has been followed for periods of months or years. Once again the methods of selection have varied and prevent an accurate assessment of the comparative incidence of sequelae and chronic cases. In the Iceland epidemic, fifty-seven (12 per cent) of the 465 patients originally affected at Akureyri were examined seven to ten months after the onset [*6*]. These patients were not representative of the epidemic as a whole, as 74 per cent of them had been paralyzed whereas the paralysis rate for the whole outbreak was only 28 per cent. Six years after the outbreak Sigurdsson [*21*] examined thirty-nine of these fifty-seven patients again (thirty-three women and six men) and reported his findings. There is no information as to what had happened to the remaining eighteen. It seems reasonable to suspect that a bias was operating in favor of patients with continued symptoms. The grounds for the selection of eight of nineteen patients for re-examination fifteen months after the New

York State outbreak [*14*] and twelve of fifty patients six months after the Bethesda epidemic [*15*] are uncertain. The follow-up studies in the Alaska [*17*] and Punta Gorda [*16*] outbreaks are important because all patients originally examined were traced and studied after the elapse of two years in the former, and of five months in the latter.

Seven to ten months after the Akureyri outbreak, Sigurdsson and his colleagues [*6*] found that most of the fifty-seven patients whom they examined had returned to work. However, only six were free of symptoms. Among the remainder, nervousness, fatigue and persistent muscular pains were common, and eleven complained of mild paresis. On examination, nineteen of the patients were found to be free of all objective evidence of disease but in the rest there was a confusing mixture of signs, some of which were thought to represent organic disease and others to indicate hysteria. Localized muscular tenderness was found in nineteen, Paresis in sixteen, muscular atrophy in fourteen and sensory changes in twelve.

Six years later, thirty-nine of these patients were examined again [*21*]. All had returned to their previous occupations (except one who was suffering from a gastric ulcer), but only five considered themselves completely recovered. Of the remainder, twenty-eight complained of nervousness and tiredness, twenty-four of muscle pains, and eight of loss of memory. Sleeplessness and paresthesias occurred less frequently. Muscular tenderness was found in ten, paresis in nine, and atrophy in six. Unfortunately, both these follow-up studies are lacking in any description of changes in tone, coordination or reflexes.

Two to three years after the acute illness, Pellew [*33*] interviewed the five Adelaide patients who had originally been chosen for virological studies. In all, there had been emotional instability or lack of concentration for eighteen months to two years, and in four, muscular pains had also been a feature. All five had improved and were well at the time of interview.

Fog [*9*] describes the enormous fluctuations in symptomatology in his Copenhagen patients during the first two to three months of the illness. Six months after the outbreak, three of the ten patients had returned to their occupations, three were working part time, two were convalescent and two were still in the hospital. None were free of symptoms, but all had improved.

In the Bethesda outbreak [*15*], none of the twelve patients selected for re-examination three to five months after the onset felt well, although they considered that they were improving slowly. They complained of recrudescences of low grade fever, myalgia, chest pains and localized weakness.

Interrogation of the Punta Gorda patients [*16*] five months after the original study demonstrated a paucity of signs as compared with symptoms, an over-all tendency towards slow improvement and a fluctuating course. Only one patient was completely well. In the remainder there had been periods of improvement interrupted by exacerbations of symptoms with a definite trend towards recovery. Thus, whereas in the second month of the disease more than half of the patients were confined to bed, only three were thus confined in the sixth month. Symptoms remained common; nervous tensions in eighteen, fatigue in fifteen, and depression in twelve. On the other hand, objective evidence of mental tension (the criteria are not described) was found in only one case. Diminution in sensation was found in ten patients, muscular tenderness in seven and paresis in one.

Deisher [*17*] appears to have had the unusual opportunity of re-examining all his 175 patients two years after the onset of the illness. Unfortunately, the information derived was incomplete; there are no data available about the number who were free of symptoms or the number who had been unable to resume work, and no description is given of reflex and sensory changes. Of the 175 patients, 110 complained of tiring easily, eighty-one of pain and stiffness, and fifty-seven of muscle weakness (as distinct from "paralysis," which was present in sixteen cases). Emotional instability, tension, poor concentration and memory defects were extremely common. Tremor, incoordination and muscular jerking were also seen.

Summary of the Clinical Features. In all outbreaks prodromal symptoms preceded the development of paresis or other neurological signs, but their severity and duration varied. In eight, the prodromal illness was well defined, and lasted about a week. In the Coventry and Durban cases it was mild and most of the patients presented for treatment in the paretic phase. In the Berlin outbreak the prodrome was sharp but abbreviated, lasting three days. The

Punta Gorda outbreak differs in the length and vagueness of the premonitory phase. Most of the patients were not confined to bed until the end of the third week. Information about the length of the prodromal illness in the New York and Alaska cases is incomplete.

Headache has been reported as a presenting feature in all outbreaks and pain in the neck, back and limbs are also common early symptoms. These complaints and the malaise which accompanies them have been out of proportion to the fever, which is usually slight even at the onset and sometimes absent [*8,12,15,16*]. Symptoms of an upper respiratory or gastrointestinal disturbance (sore throat, coryza, nausea, vomiting, diarrhea) may also develop at this stage. A definite intermission between the prodromal symptoms and the paretic illness is rare, and has been reported as a constant feature in only one outbreak [*15*].

Muscular pain, headache or pain in the neck, and paresis have been features of the fully developed syndrome in all outbreaks. In the worst Los Angeles, Middlesex and Royal Free Hospital cases, the myalgia has been agonizing, requiring administration of narcotics for its relief. Its variability both in site and in intensity from day to day has been remarked on a number of occasions. Pain in the limbs has occurred at some stage in most cases, but pain in the shoulders, chest and abdomen is also a prominent feature, and has raised the question of a Coxsackie infection. In the New York State and Coventry cases the discomfort in the limbs scarcely amounted to pain.

With the exception of the New York cases the distribution of the paresis has followed that of the muscle pain and tenderness. Numbness, tingling and in some cases deficiencies of sensation on formal testing have been a feature of all outbreaks except one [*11*], and usually occurred in limbs affected by paralysis. Hyperpathia, muscular spasm, cramps, tremors and involuntary movements were noted in severely affected patients in about half the outbreaks. The deep reflexes in the paretic limbs may be hyperactive or depressed, but are rarely if ever abolished. Frank extensor plantar responses have been unusual, but equivocal or absent responses are relatively common. Retention of urine requiring catheterization or incontinence has occurred in eight outbreaks, and urinary frequency was a feature of one other.

Symptoms or signs indicating damage to the cranial nerves or their central connections have occurred in nine outbreaks. In six they were uncommon, but in the Royal Free Hospital Middlesex and Los Angeles cases they were relatively frequent. Diplopia, facial paresis, tinnitus, vertigo, inner ear deafness and bulbar involvement have all been reported. Hyperacusis was a feature of no less than five epidemics [*7,8,11,12,17*]. Nystagmus was almost invariable in the Middlesex Hospital and Berlin patients, common in the Royal Free Hospital cases, and an unusual finding in four other outbreaks. Mental disturbances, of which depression, emotional lability and lack of concentration are commonest, have occurred in all reported outbreaks. In most instances they appeared during the acute illness [*5,8,12,14–18*] but in others they first became manifest during convalescence [*6,7,10*].

Lymphadenopathy was first reported by White and Burtch [*14*] in four of the New York State cases. It also occurred as a rare feature in the Durban and Middlesex Hospital cases. In the Royal Free Hospital outbreaks it was such a contant feature that the illness was at first diagnosed as infectious mononucleosis. Hepatic enlargement was also noted in a few of these cases.

In most patients recovery has been complete within one to two months. However, in a proportion, which has varied from outbreak to outbreak, the course has been punctuated by relapses. These have involved simply a return of pain and fever in some instances, in others, fresh paresis and other neurological signs, or mental disturbances. In general, even in these patients there has been a trend towards improvement but in some instances a characteristic syndrome of chronic ill health has developed, with cyclical recrudescences of pain, fatigue, weakness and depression, often coincident with menstruation, cold weather and exertion. Objective neurological sequelae, such as muscular atrophy, involuntary movements, sensory loss, deafness and incoordination have occurred in a small minority.

SPORADIC CASES

In addition to epidemics, sporadic cases with the familiar clinical features have occurred. The first endemic case in which a diagnosis of "Iceland disease" was made was reported by Hardtke [*28*]. He described the illness of a forty-one year old female physiotherapist in

Indiana in October 1953. She presented with headache, stiff neck, pain in the shoulders and limbs, and incoordination. Within a few days she found that attempted movements or the slightest jolting precipitated agonizing cramp-like muscular spasms against which her only defense was absolute immobility. She was admitted to the hospital as a poliomyelitis suspect and on examination was found to have questionable weakness of the lower left side of the face and exaggerated unequal reflexes. The cerebrospinal fluid was normal, and in the absence of any flaccid paralysis, a diagnosis of poliomyelitis could not be sustained. A relapse occurred in February 1954, and when examined in July she was found to be depressed, with loss of memory and absent gag reflex on the right, diminished sensation on the left side of the body and persistence of the reflex abnormalities already described. Coxsackie infection was not excluded in this instance, although the combination of neurologic signs with a normal cerebrospinal fluid and a chronic course make this diagnosis unlikely.

In 1956 Ramsay and O'Sullivan [*29*] reported on eight patients admitted to the Infectious Diseases Department of the Royal Free Hospital from the population of northwest London between April and October 1955, before, during and after the extensive epidemic in the staff of the main hospital. None of these patients, of whom seven were female, had been in contact with the sick nurses.

The onset was generally gradual with headache, pain in the limbs, giddiness and upper respiratory or gastric symptoms. Fever rarely exceeded 100°F. Earache, tinnitus, cramps, muscular twitching, tremors and parasthesias were also noted. On examination, lymphadenopathy occurred in seven; stiffness of the neck, paresis and exaggerated deep reflexes in six; sensory impairment and muscle tenderness in five; and cranial nerve involvement in four. Extensor plantar responses were noted in three cases. Convalescence was protracted. In four cases it was complicated by emotional disturbances. Full virological studies, including the use of tissue culture methods, were carried out in all eight cases and were negative.

Jellinek [*30*] described two patients on the staff of a hospital in Hampshire who suffered from a similar illness in the summer of 1955. Both were females, one a doctor and the other a nurse. Both had headache, stiffness of the neck, fever, myalgia and a variety of neurological signs, including nystagmus (two), facial weakness (one), exaggerated reflexes (two), clonus (one) and sensory changes (one). There were two well defined relapses in each case in which retention of urine, requiring tidal drainage, was a distressing feature. Lymphadenopathy occurred in one case. In both, emotional lability was noted. Repeated examination of the cerebrospinal fluid revealed no abnormality. Virological studies were incomplete.

Galpine and Brady [*32*] reported seven cases which arose sporadically in the Coventry area in the late summer and fall of 1956, three years after the outbreak in their nursing staff. Four patients were female and three male. The early symptoms (sore throat, lassitude, drowsiness, vomiting, nuchal pain, backache, giddiness and headache) were similar to those reported elsewhere. Paresis was found in all cases and tended to fluctuate and shift. It was usually accompanied by aching, paresthesias and tenderness. Alterations in tone were rare, but twitching, cramps, involuntary movements and tremors occurred. The reflexes were brisk and the plantar responses difficult to obtain. The sensory changes noted included hyperpathia, hypoasthesia, anesthesia and astereognosis. Difficulty in starting micturition occurred in three cases and incontinence in one other. Shotty lymph nodes were found in the posterior triangle of the neck in three. Of six patients who were examined three months after their discharge from the hospital, two had recovered completely. The remainder complained of myalgia, weakness, parasthesias and diminished mental grasp. Examination of the feces in three cases failed to show any evidence of a cytopathogenic agent, and serological tests for poliomyelitis were negative.

In a second paper, Ramsay [*31*] reviewed his experience with thirty-four patients admitted from northwest London between April 1955 and December 1957. Headache was an almost universal symptom, and pain in the limbs, giddiness and pain in the neck occurred in about half of the patients. Lassitude, subjective sensory phenomena and back pain occurred in about a third, and sore throat, earache and cramps were less frequent. On general examination conjunctivitis and evidence of an upper respiratory infection were noted in one-third, and enlarged lymph nodes in one-fourth of the patients. In the nervous system, definite evidence

of paralysis occurred in 50 per cent. Exaggerated deep reflexes, sensory disturbances and muscular tenderness were also prominent. Nystagmus and extensor plantar responses were found in about one-fifth. Cranial nerve lesions, tremors and myoclonus occurred in four patients. Low pyrexia was the rule. Results of serological tests for lymphocytic choriomeningitis, mumps, leptospirosis and poliomyelitis were negative in each case. Throat washings and feces were also examined.

Other Unexplained Outbreaks. Other problematic outbreaks have been described which share some of the characteristics already outlined. Bond [*34*] mentions briefly an outbreak of 463 cases in Tallahassee, Florida, in the fall of 1954. The disease, which was selective for married white women, was characterized by disturbances of mood, transient paresis, parasthesias and relapses. This outbreak, and that reported by Wallis [*35–37*] from Cumberland, England, are probably similar to those already described but sufficient data have not been published on which to base a definite opinion.

Rose [*38*] and Wright and Morley [*39*] have reported epidemics of obscure encephalitis in West Africa, and have referred in their discussions to the outbreaks already described. In the former, which occurred in Sierra Leone, the onset resembled cholera with high pyrexia and prostrating diarrhea and vomiting, and the course was fulminating with terror, severe myalgia and vertigo. Pains around the costal margin similar to those of Bornholm disease were a common feature. A little less than one-third of the patients died. The cerebrospinal fluid was normal.

The outbreak in Nigeria, described by Wright and Morley [*39*], was characterized by low fever, tremor, aphasia, a normal cerebrospinal fluid and a favorable outcome in all cases. Certain of the epidemiologic features suggested an intoxication.

Other than an unknown etiology, the predilection of the agents for the nervous system, and a normal cerebrospinal fluid, neither of these outbreaks resemble those described in this paper.

McConnell [*40*] reported sixteen cases of illness among the student nurses of the University Hospital of Pennsylvania in 1945. Severe headache was invariable, hyperesthesia occurred in thirteen, meningism in twelve, and pleurodynia in ten. A diagnosis of epidemic pleurodynia (Bornholm disease) was made, although the clinical picture was considered to be atypical. A low grade fever accompanied by "disproportionate severe generalized headache and myalgia" persisted for several weeks in five cases, and in two there were four and five relapses, respectively. Stupor and episodes of loss of consciousness occurred in one patient and sensory loss in another. The sequelae were headache, myalgia and pleuritic pain. Of five patients examined a mild pleocytosis was found in the cerebrospinal fluid in two. The similarities which this outbreak shares with the fourteen already described are obvious. However, in view of the absence of paresis, and the fact that the outbreak preceded the isolation of the Coxsackie viruses which could thus not be excluded in this instance, it has been classified separately.

Hook's [*41*] report from Hygiea, Sweden, underlines the nosological difficulties in this field in the absence of pathological support. Under the title "Iceland disease" he described four cases in the staff of a hospital in the summer of 1956. The affected persons, of whom two were physicians, worked in a "single room." (It is not clear whether this was a laboratory or a clinic.)

The first patient's illness developed gradually with mild muscular aches, paresthesias and weakness in the hands and feet. The paresis progressed over a period of several weeks and was accompanied by flaccidity and diminished reflexes. Mental depression was a feature in the later stages. Lumbar puncture in the second month of his illness revealed a protein of 60 mg. per cent, with a normal cell count. Electromyography showed the typical picture of denervation and a provisional diagnosis of infective polyneuritis was made. Polio and Coxsackie viruses were searched for without success. Vague illnesses characterized by headache and paresthesias subsequently developed in the patient's family.

The second patient's illness, which developed four weeks later, was acute. Three days after the onset of myalgia and paresthesias she had fever, indefinite stiffness of the neck and weakness of the legs. Within a further four days flaccid paralysis of the lower limbs was virtually complete. It had not regressed eight weeks later, and no fresh signs had developed. Lumbar puncture shortly after the onset showed 44 polymorphonuclear leukocytes, 52 lymphocytes and 90 mg. of protein. The suspicion that this case was, in fact, poliomyelitis is not dispelled by the failure to isolate polio virus from

the stools in the fifth week. An unconvincing twofold rise in antibody titre against type 2 polio virus was demonstrated between the seventh and twenty-first day. The Coxsackie virus was not found. The third and fourth patients described by Hook suffered indefinite illnesses characterized by fatigue and paresthesias but exhibited no physical signs.

Hook's outbreak is difficult to classify. The localization of four cases to a small segment of a community suggests a common etiology. However, although the second case is clinically consistent with a diagnosis of poliomyelitis, the first with its slowly progressive paraplegia and sensory loss is not. The flaccidity of the paralysis, the failure to improve, and the electromyographic picture of denervation (Case I) are features quite unlike the cases reported from Los Angeles, the Royal Free Hospital and elsewhere. Cases III and IV resemble the milder cases reported from these outbreaks. In our present state of ignorance it may be well to suspend judgment on this outbreak.

LABORATORY INVESTIGATIONS

The Peripheral Blood. Examination of the cells of the peripheral blood has been, on the whole, unrewarding. Anemia has not been reported. In eight outbreaks [*5,6,8,10,14,16–18*] the total and differential white counts have been normal in most cases.

A special study of the leukocytes was made in the first Royal Free Hospital epidemic [*12*], a total of 750 specimens being examined from more than 400 confirmed or suspected cases. In addition, smears from 138 selected patients were examined by three independent observers. No specific changes were found. In about half the cases, relative lymphocytosis was seen during the early course of the illness. Occasional abnormal lymphocytes (Türk and plasma cell-like forms) were noted in some patients, but the changes characteristic of infectious mononucleosis did not occur. Similar findings have been reported in the endemic cases in the neighborhood of the Royal Free Hospital [*29,31*]. The authors stress the point that the changes are not specific, and are identical to those seen in virus infections, such as poliomyelitis and the common cold. A relative lymphocytosis was also observed in one-third of the Bethesda cases. The small Berlin outbreak differed in that a polymorphonuclear leukocytosis occurred in all seven patients (range 9,700 to 15,300 cells per cu. mm.).

Information about the erythrocyte sedimentation rate is incomplete. In the Royal Free and Middlesex Hospital outbreaks it was normal. In the Alaska outbreak it was raised in the few patients in whom it was performed.

A positive agglutination reaction to washed sheep erythrocytes (Paul Bunnell test) is extremely uncommon [*14*] and when present further studies have suggested a remote infection.

The Cerebrospinal Fluid. The cerebrospinal fluid is known to have been examined in 199 cases in eleven outbreaks in which exact figures are available. The number of additional cases examined in the Durban and Alaska outbreaks is not recorded; lumbar punctures were not performed in the second Royal Free Hospital outbreak.

The cells: Normal cell counts (less than 5 cells per cu. mm.) have been the rule in all outbreaks except those in Iceland [*6*] and Alaska [*17*]. At Akureyri, two of five patients studied showed mild lymphocytosis, as did three others examined at Reykavik. In Alaska the total number of examinations is not stated but it appears that in two-thirds of those studied counts of 10 to 30 cells were found. In the remaining ten outbreaks in which exact figures are available, lumbar punctures were performed in 194 cases and less than 5 cells were observed in 180 of these (92.8 per cent). In the other fourteen cases (7.2 per cent) the cell counts ranged from 6 to 66 lymphocytes. In sporadic cases the results have been similar. Of twenty-seven cases studied, normal cell counts were found in twenty-five, a mild lymphocytosis in two.

Protein: Protein estimations were made in 194 cases in ten epidemics. In 182 cases (94.6 per cent) concentrations of 40 mg. per cent or less were found, and in the remaining eleven (5.4 per cent) the readings varied from 48 to 85 mg. per cent. In addition, we have the observation that in the Durban outbreak, abnormal concentrations of protein were "very rare." There is no information about the Alaska outbreak. Of twenty-seven sporadic cases examined, protein concentrations ranged between 50 to 80 mg. per cent in 4 cases; in the remainder the protein concentrations were less than 40 mg. per cent.

Apart from an occasional weakly positive Pandy test, no other abnormalities have been reported in the cerebrospinal fluid.

Creatinuria. White and Burtch [*14*] studied the excretion of creatine in thirteen patients.

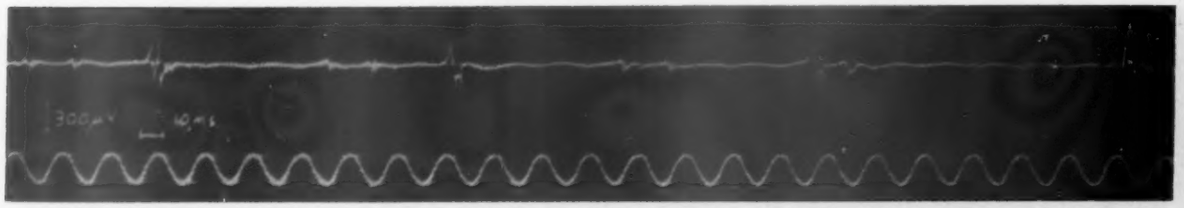

FIG. 2A. Recording from severely involved tibialis anterior muscle on maximal sustained volition. Recordings with concentric needle electrode and maximal sustained volition.

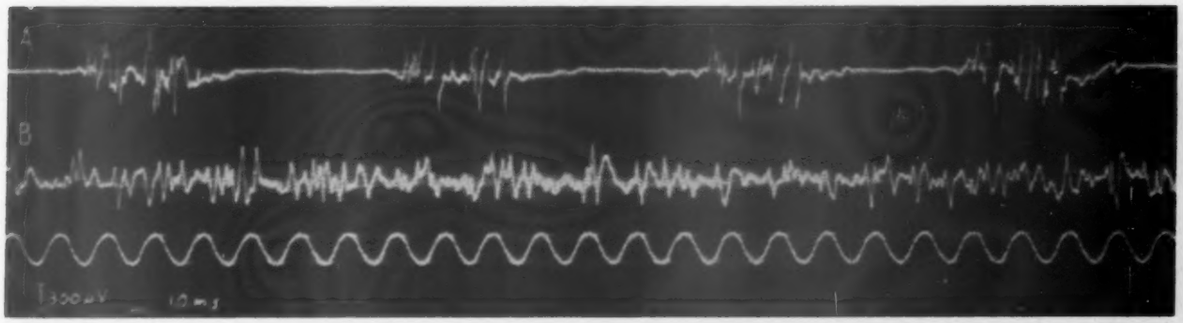

FIG. 2B. Recordings with concentric needle electrode and maximal sustained volition. A, from weak tibialis anterior muscle. B, from normal contralateral tibialis anterior muscle. Calibration 50 cycles. 300 microvolts. (From: *Brit. M. J.*, 2: 895, 1957.)

In twelve the urinary output was more than 100 mg. daily and in eight of these it exceeded 200 mg. It was considered that the findings could not be explained on the basis of physiological creatinuria as there were no athletes with exceptional muscular development in the group, and only one child. Creatine studies have not been reported by other workers.

Electromyography. Electromyographic studies were performing in two patients in the Copenhagen outbreak in 1952. Unfortunately, no description of the tracings is given. They were interpreted as showing "neurogenic weakness of peripheral or radicular origin." Macrae and Galpine [*10*] were the authors who first drew attention to a consistent electromyographic pattern in affected muscles on voluntary movement, which has subsequently been confirmed by Richardson [*42*] and Ramsay [*31*].

According to Richardson, who studied twenty-eight patients with marked motor involvement from the Royal Free Hospital outbreak, the strength-duration curves of the involved muscles were normal in all cases except one. Nerve conduction measurements were within normal limits. Evidence of lower motor neurone degeneration was therefore exceptional. Similar results were reported by Alexander [*43*] who performed nerve conduction studies on twenty patients from Durban.

Electromyography early in the disease revealed fasciculation potentials. With the onset of paresis an abnormality of recruitment occurred similar to that which has been described in involvement of the motor units at the level of the cord by Bauwens [*44*]. On volition, the number of motor unit potentials was severely reduced and in some instances the movement was initiated by prolonged polyphasic potentials. However, the accompanying evidence of nerve fibre degeneration which might be expected in a protracted lesion of the motor neurone was not obtained.

During recovery, Richardson found changes similar to those described by Macrae and Galpine [*10*]. On volition the motor unit potentials were grouped in sequences lasting from 50 to 80 milliseconds, with regular intervals of complete inactivity giving rise to a tremulous contraction at a frequency of 5 to 10 per second. Ramsay and O'Sullivan [*29*] studied eight sporadic cases and reported similar findings. On electromyographic exploration of affected muscles, voluntary movement produced action potentials in groups of the same duration and frequency as those reported by Richardson. The similarity of the findings in the Royal Free Hospital cases and Ramsay's material is strikingly demonstrated in Figures 2 and 3. In his later review of thirty-four cases, Ramsay

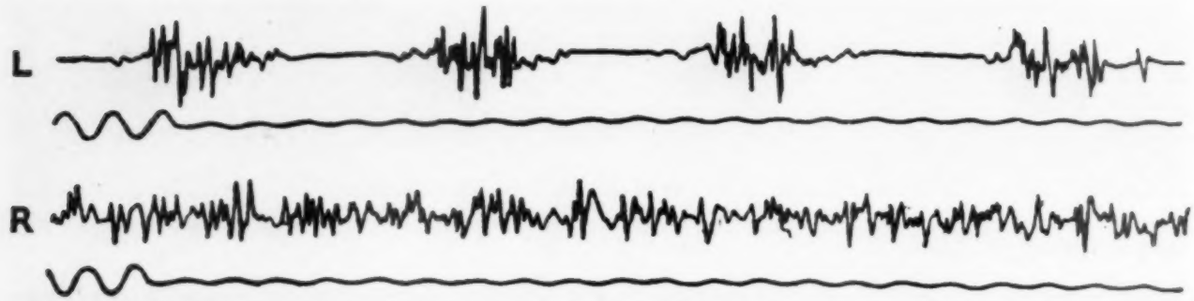

FIG. 3. Electromyograms: upper register, from left (affected) tibialis anterior muscle on maximal volition, showing grouping of large polyphasic motor-unit potentials; lower register, from right (unaffected) tibialis anterior muscle on maximal volition, showing complete interference pattern of normal motor-unit potentials. Calibration 500 and 100 μV at 50 cycles per second. (From: RAMSAY, A. M. *Lancet*, 2: 1196, 1957.)

[*31*] reported that twenty-one of twenty-six patients examined electromyographically (including the eight originally described) had shown the changes described. Galpine and Brady [*32*], reporting seven sporadic cases from Coventry, found a reduction in the number of motor unit potentials and grouping in all five patients examined. Polyphasic and abnormally large potentials were also found.

Electroencephalography. Electroencephalograms have been studied by Fog [*9*], Ramsey and O'Sullivan [*29*], Galpine and Brady [*32*] and Poskanzer et al. [*16*]. Some non-specific abnormalities were reported in patients with behavior disorders by Ramsay and O'Sullivan. In all other cases the electroencephalogram has been normal.

ETIOLOGICAL STUDIES

Virology. In view of the dissimilarity of the clinical picture to any known bacterial infection, attention has naturally been focussed on isolating a virus as the responsible agent. (Table II.) In nine of the fourteen outbreaks unsuccessful attempts were made to isolate the poliomyelitis and Coxsackie viruses. In the Middlesex Hospital outbreak [*8*] polio virus Type 3 was isolated from the feces of one case. However, in view of the failure to isolate any detectable antibody from serial specimens of this patient's serum,

TABLE II

ATTEMPTS TO ISOLATE VIRUS

Location	No. of Cases Examined	Pathological Material Studied	Animal Species	Tissue Culture Material
Los Angeles	0	Nil	Nil	Nil
Iceland	12	Blood, C.S.F., feces	Guinea pigs, hamsters, mice, suckling mice, monkeys	.....
Adelaide	5	Blood, C.S.F., throat washings, feces	Monkeys, suckling mice, weaned mice	Embryonated hen eggs
New York State	17	Feces, throat washings	Monkeys (2), suckling mice (15)	.....
Middlesex Hospital	3	Feces	Monkeys, suckling mice	Monkey kidney, monkey testicle
Copenhagen	0	Nil	Nil	Nil
Coventry Hospital	5	Feces	Guinea pigs (2), adult mice, suckling mice, monkeys (2) rabbit (1)	Human embryonic muscle and skin; monkey kidney, monkey testis
Bethesda Hospital	?	Blood, C.S.F., throat washings, feces	Suckling hamsters (9), adult mice (26), suckling mice (40)	Human HeLa (28), chorion (20), fibroblasts (10), monkey kidney (28), monkey testicle (31)
Seward, Alaska	0	Nil	Nil	Nil
Berlin	4	Feces	Inoculated into mice and tissue cultures were set up for Coxsackie and polio virus	
Durban Hospital	?		Extensive virological studies negative	
Royal Free Hospital (1)	?	Blood, throat washings, feces	Ferrets, guinea pigs, suckling hamsters, adult mice, suckling mice, monkeys	Fertile hen eggs, HeLa cells (9); human embryo brain (2), liver (1), spleen (1), kidney (6), human infant kidney (3), monkey kidney (10)
Punta Gorda	19	Blood clots, throat washings, feces	Suckling mice	HeLa, human liver, monkey kidney
Royal Free Hospital (2)	0	Nil	Nil	Nil

NOTE: Number of experiments, where given, indicated in parentheses. C.S.F. = cerebral spinal fluid.

TABLE III

SEROLOGICAL STUDIES

Location	A.P.C. virus	Brucellosis	Coxsackie	Encephalitis Eastern Equine	Encephalitis Japanese B	Encephalitis Western Equine	Encephalitis St. Louis	Encephalomyocarditis	Herpes Simplex	Influenza A	Influenza B	Influenza C	Leptospirosis	Louping Ill	Lymphocytic Choriomeningitis	Mumps	Paracolon (Bethesda-Ballerup)	Polio Virus	Psittacosis	Q Fever	Rabies	Rickettsia Burneti	Toxoplasmosis
Los Angeles	..	....	....	Nil		....	....	....	..	....	..	..	....	..	....	....	....	....	..	....	....	..	..
Iceland	..	....	....	0 (12)	0 (12)	0 (12)	0 (12)	....	..	0 (12)	..	..	....	..	0 (12)	....	....	....	..	0 (12)	0 (12)	..	..
Adelaide	..	....	....	....	....	....	....	0 (5)	..	....	..	..	0 (5)	..	0 (5)	0 (5)	....	0 (5)	..	....	....	..	..
New York State	..	....	0 (17)	....	....	....	....	....	..	....	..	..	....	..	....	....	....	0 (17)	..	....	....	..	..
Middlesex Hospital	..	....	....	....	....	....	....	....	..	....	..	..	0 (8)	..	0 (8)	* (8)	....	3† (10)	..	....	....	..	..
Copenhagen	..	....	....	Nil		....	....	....	....	....	..	..	....	..	....	....	....	....	..	....	....	..	..
Coventry Hospital	..	....	....	....	....	....	....	0 (10)	..	....	..	..	0 (10)	..	0 (10)	* (10)	....	0 (10)	..	....	....	..	..
Bethesda Hospital	0 (7)	† (13)	0 (5)	....	....	....	....	....	..	....	..	..	....	..	....	....	See text	....	..	....	....	..	..
Seward, Alaska	..	....	....	....	....	....	....	....	..	....	..	..	....	..	....	....	....	† (19)	..	....	....	..	..
Berlin	..	0 (7)	....	....	....	....	....	....	..	0 (7)	0 (7)	..	....	..	....	....	....	....	..	....	....	..	..
Durban Hospital	..	....	....	No details known					..	....	..	..	....	..	....	....	....	....	..	....	....	..	..
Royal Free Hospital (1)	0 (?)	....	....	....	....	....	....	0 (6)	0 (?)	0 (?)	0 (?)	0 (?)	0 (?)	0 (?)	....	0 (?)	....	....	0 (?)	....	....	0 (?)	0 (?)
Punta Gorda	..	0 (12)	....	0 (12)	....	0 (12)	0 (12)	....	..	....	..	..	0 (12)	..	0 (12)	* (12)	0 (12)	....	..	....	....	..	..
Royal Free Hospital (2)	..	....	....	Nil		....	....	....	..	....	..	..	....	..	....	....	....	....	..	....	....	..	..

NOTE: Figures indicate number of positive tests; in parentheses, number of cases studied.
* Immune bodies in titres suggesting remote infection found in some cases.
† The findings were of doubtful significance and are discussed in the text.

the extremely unusual clinical picture (bilateral perceptive deafness developed), and a normal cerebrospinal fluid, it was concluded that this virus was probably not responsible for her illness. Table II shows that unsuccessful attempts have also been made to isolate other viruses in a number of outbreaks. Particularly extensive investigations were carried out in the Bethesda and Royal Free Hospital epidemics.

In four outbreaks no attempts to isolate a virus were made; one of these was the small second Royal Free Hospital outbreak [*13*], which was regarded as clinically identical with the large epidemic which had been the subject of extremely extensive virologic studies the previous year. In the Seward outbreak [*17*] the only investigation performed consisted in random serological studies in nineteen patients who were experiencing subacute symptoms, revealing that the "neutralization titres against the three types of poliomyelitis virus were generally low and showed no consistent pattern." In the Los Angeles [*5*] and Copenhagen [*9*] outbreaks no virological studies were made.

Serological studies (Table III) have also been widely performed. Immune bodies to the mumps virus in titres suggesting remote infection were found in a few cases. In the Bethesda outbreak [*15*] thirteen serum pairs were examined for antibodies against polio virus. A questionable fourfold rise in the titre occurred in three cases, one against each of the three types of virus. Otherwise, serological tests have been uniformly negative.

Bacterial Studies. In the Bethesda outbreak the prominence of diarrhea as an early symptom directed attention to the possibility of an enteric infection. Organisms of two strains of the Bethesda-Ballerup paracolon group were isolated from feces from twelve of thirty-eight nurses examined and from only one of fifty-four persons who were on the hospital staff at the time of the epidemic and remained well. H and O serum agglutinins against the Bethesda-Ballerup group (at a titre of 1:40 or more) were found in twenty-two of forty-seven affected nurses and in three of twenty-seven control subjects. In eleven affected nurses a rise and fall in titre was demonstrated during the period of observation. A kitchen girl who had started

work one week before the onset of the epidemic was the only person in the entire study who showed both serological strains of organism in her stools. Examination of sixty asymptomatic nurses three to seven months after the end of the epidemic revealed antibody titres in two cases, but no positive cultures.

There is thus strong circumstantial evidence to suggest that the Bethesda-Ballerup paracolon organisms were related to the epidemic of clinical illness among the nursing staff. However, in the absence of other evidence (1) that a disease can be transmitted by these organisms either in man or in animals, (2) or that they produce a neurotoxin, it is premature to conclude that they caused the epidemic. As Shelokov and his colleagues have themselves suggested, the findings may indicate simply that fecal contamination of food was occurring in the hospital kitchen at the time of the epidemic. It is possible that an unknown causative organism was being spread in addition to the Bethesda-Ballerup organism.

It is important to note that attempts to isolate paracolon organisms from patients during the Punta Gorda outbreak were unsuccessful [*16*].

Poisons. In view of the apparent predilection for hospital staffs, the question has arisen whether or not the disorder may be due to an occupational toxic hazard. This possibility received particular attention in the Royal Free Hospital outbreak [*27*]. Insecticides, paints and detergents received scrutiny, with negative results. Similar studies were negative in the Durban outbreak [*18*] and at Bethesda [*15*].

THE CASE FOR A CLINICAL ENTITY

It is significant that the first review of the syndrome under discussion was entitled, "Not poliomyelitis" [*45*]; the second, "A new clinical entity?" [*22*]. In later articles entitled, "Epidemic myalgic encephalomyelitis" [*46*], "Benign myalgic encephalomyelitis" [*46a*] and "Epidemic neuromyasthenia" [*15,16*], the authors considered themselves on sufficiently strong ground to describe and name the syndrome. This sequence indicates that the first and minimum requirement in the definition of an entity is the essentially negative one of showing that the syndrome is not an unusual manifestation of a disease already recognized. Later, as evidence accumulates, it may be possible to define the disorder in positive terms.

Poliomyelitis. In nine outbreaks an initial diagnosis of poliomyelitis was made. In favor of this diagnosis were the mode of onset in many cases (headache, pain in the neck and myalgia), the development of paresis and the season of the year. The low or absent fever, so unusual in poliomyelitis at the beginning of the paretic phase, and the rarity of a biphasic illness were at first discounted. However, other atypical features made their appearance in the later stages of the illness in such frequency that the diagnosis of poliomyelitis was withdrawn. In the second and third weeks the distinguishing features were (1) a longer active course with the development of fresh neurological symptoms and signs later than occurs in poliomyelitis, (2) the prominence and persistence of sensory phenomena, (3) the retention or exaggeration of deep reflexes in the paralyzed limbs, and (4) the normal cerebrospinal fluid in most cases.

In some outbreaks the persistence of muscular pain after the development of paresis [*47*], the occurrence of tremors and involuntary movements, and the high incidence of retention of urine in the absence of severe paralysis [*48*] were further points against the diagnosis of poliomyelitis at this stage.

The subsequent subacute and chronic course of the disorder, with its mental symptoms and partial or complete remissions and exacerbations, is quite distinct from poliomyelitis which runs its active course within a week of the onset of the major illness. With the exception of the Iceland epidemic, muscular wasting in patients with persistent paralysis has been extremely rare and in such patients no electromyographic evidence of denervation has been found. The over-all mortality in more than 1,000 cases has been nil. From the clinical point of view, the differences from poliomyelitis become progressively clearer as the illness develops.

Epidemiologically, the high attack rates (Table 1) and the predilection of the disorder for small semi-closed communities are also against the diagnosis of poliomyelitis.

The final evidence lies in the laboratory findings. In spite of careful search in ten of fourteen outbreaks, poliomyelitis virus was found in only one case [*8*] and in this patient no detectable antibodies appeared in the blood.

Other Enteric Viruses. There is now good evidence that enteric viruses of the Coxsackie group [*49*] cause epidemic pleurodynia [*50*] and encephalomyocarditis in babies [*51*]. Viruses of the Coxsackie and Echo groups have also been re-

covered from cases of aseptic meningitis [*52*] and lower motor neurone type paralysis.

Scrutiny of reports claiming that they have been concerned in outbreaks of encephalitis in adults shows that objective evidence of damage to the central nervous system has, in fact, been the exception rather than the rule [*53,54*].

In the outbreaks reported here certain clinical similarities with epidemic pleurodynia, notably the occurrence of pleuritic chest pain in six outbreaks, of abdominal pain in six, and pain in the shoulders in twelve, stimulated a search for these viruses. In nine outbreaks material was injected into suckling mice with negative results (Table II); and in five instances [*8,10,12,15,16*] tissue cultures of kidney cells from monkeys failed to grow Echo viruses. In other respects, notably the mental symptoms and the chronicity of some cases, the outbreaks reported here are unlike any that have been found to be associated with Coxsackie or Echo viruses.

Encephalitis Lethargica. The occurrence of tremors, myoclonus or other involuntary movements in a few cases in seven outbreaks raised the question of the reappearance of encephalitis lethargica in epidemic form. Although this disease was notably pleomorphic [*55*], it has certain distinct clinical and epidemiologic features, which are not shared by any of the outbreaks reported here. According to Von Economo [*55*] it occurred chiefly in the first three months of the year, was of low infectivity, with no sex predominance and a high mortality. Postencephalitic Parkinsonism occurred in about 30 per cent of all recognized cases. This complication has not been recorded in the illness described here, although one Royal Free Hospital patient had choreoathetoid movements of the right arm with cog-wheel rigidity some months after the acute illness. Involuntary movements have also been reported in the chronic stage in a few of the Alaskan cases [*17*]. Delinquent behavior, such as occurred after encephalitis lethargica epidemics, has not been described.

The Arthropod-Borne Encephalitides. The various arthropod-borne encephalitides have common epidemiological and clinical features which distinguish them from the syndrome reported here. As might be expected, these diseases occur most frequently in field and forest workers who are exposed to the bites of mosquitoes, ticks, and bird and animal parasites [*56*], and evidence of spread by personal contact is uncommon. The various types of insect-borne encephalitis share an acute onset with high fever and headache, followed in severe cases by delirium, convulsions, tremors and spastic paralyses. Death occurs within ten days in a variable proportion. A pleocytosis of 100 to 500 cells in the cerebrospinal fluid and a polymorphonuclear leukocytosis in the peripheral blood are characteristic.

The syndrome described in this paper, with its institutional outbreaks, evidence of spread by personal contact [*5,6,12*], absence of delirium or convulsions, predominantly normal cerebrospinal fluid and absent mortality, is in striking contrast. From the virological point of view, the agents of the insect-borne encephalitides are best recovered from nervous tissue which was not obtained from this material. However, a search for antibodies against some of the known types of encephalitis virus was made in the Iceland [*6*] and Punta Gorda [*16*] outbreaks and against louping ill (Russian spring-summer encephalomyelitis) in the Royal Free Hospital cases [*12*] without success.

Infectious Mononucleosis. A diagnosis of infectious mononucleosis was seriously entertained at the onset of the Royal Free Hospital outbreak [*57*]. In favor were the known predilection of this disease for hospital staffs, the lymphadenopathy, and the presence of a few atypical lymphocytes in the peripheral blood in some cases. A wide variety of neurological manifestations have been described in infectious mononucleosis, but these are rare. As the epidemic developed, the overwhelming frequency of neurological symptoms and signs made this diagnosis unlikely, and the failure to demonstrate typical Downey cells or significant titres of heterophile antibodies finally excluded it.

Other Infections. Searches for a wide variety of other agents have been carried out (Tables II and III) without success.

The Question of Hysteria. The question of hysteria has been raised in five outbreaks [*5,6,9,12,20*] and by Galpine and Brady [*32*] and Ramsay [*31*] in the discussion of their endemic cases. Most authors agree that hysterical manifestations have occurred in a few patients [*5,9,31*], particularly in the later stages [*12*], but none has felt that it has contributed significantly to the pattern of the disease.

In an illness in which there has been a selectivity for young women, no mortality, and few positive laboratory findings, it is important to examine the possibility that hysteria may have accounted for part or all of the clinical picture

more closely. Epidemic hysteria has been recognized for many centuries as a particular hazard in institutions containing women [*58*]. It has presented in many bizarre ways from the mass compulsive dancing (St. Vitus Dance) of the middle ages, to the "quaking" of the early Quakers, the fits of Wesley's converts and the effort syndrome of soldiers in the 1914–1918 World War. The form and content of the manifestations depend upon the ideas and fears of the age [*59*].

No one can seriously contend that every patient in all the outbreaks described in this paper has been hysterical. The presence of definite ocular, facial and palatal pareses, or nystagmus, and of extensor plantar responses in rare instances, and a definite pleocytosis in the cerebrospinal fluid in a few cases indicate organic disease of the nervous system in a minority at least, unless we are to doubt the competence of a number of different observers.

A more reasonable viewpoint would be that the majority of the cases constitute a hysterical reaction to a small number of cases of infection of the nervous system, for example, poliomyelitis. Thus it will be readily admitted that an epidemic of poliomyelitis, such as occurred in Los Angeles in 1934, would produce overwork and emotional strain in the nursing staff of the hospital concerned. Many of the nurses would naturally feel apprehensive about becoming ill with the disease, and might be inclined to misinterpret the minor aches and pains of every day life. With the development of a few genuine cases of poliomyelitis among the staff and the resulting increasing tension, it is possible to envisage an epidemic of hysterical paralysis.

An attractive case could be made for such a hypotheses. The high attack rates in the most suggestible groups of the community, the predilection for hospital staffs, and the association with preceding or concurrent outbreaks of poliomyelitis might thus be explained. Clinically, the absent or insignificant fever, the prominence of sensory phenomena, which are admittedly often of bizarre distribution and content [*13,15*], the fluctuation of symptoms and signs from day to day, and the high incidence of negative cerebrospinal fluid findings would also fit in with this hypothesis. Further support might be obtained from the peculiar nature of the paresis. Paralysis without the disappearance of tone and deep reflexes and subsequent atrophy on the one hand, or true spasticity and extensor plantor responses on the other, is suspicious of hysteria. As Brain [*60*] has pointed out, inability of the patient to relax the affected limb in such cases may cause the deep reflexes to appear exaggerated. Tremors on volition and involuntary movements may also be present in such patients. A jerky contraction against resistance is often prominent [*60*]. If we add muscle pain and tenderness, which are admittedly uncommon in hysterical paralysis, such a description resembles closely the features of the paralysis in the Royal Free Hospital cases [*12*] which were attributed to a deep subcortical lesion, and is similar to those described in many less detailed reports.

There are also strong arguments against the idea that the syndrome constitutes a mass hysterical reaction to a few cases of poliomyelitis. In the first place, in the minority who had undoubted objective physical signs, the clinical picture was quite unlike poliomyelitis. In this minority, nystagmus [*7,8,9,12,18,19*], ophthalmoplegia [*8,12*], facial palsy [*5,7,9,12,18,19*], palatal paresis [*5,8,12*] and extensor plantor responses [*8,9,12*] were recorded, but true flaccid paralysis with absent reflexes did not occur, and subsequent atrophy was recorded with any frequency in only one outbreak [*6*] and in exceptional instances in two others [*5,12*]. In addition, these patients shared the other characteristic features, namely myalgia, sensory changes, low pyrexia, mental symptoms, and a chronic or relapsing course, which were experienced by the majority of patients who had no truly objective physical signs. Thus we would be forced to the conclusion, on this hypothesis, that even the patients with objective findings were also suffering from hysteria. This seems unlikely.

In the second place, the relationship to poliomyelitis is not constant. At the Royal Free Hospital no patient with poliomyelitis had been admitted to the hospital prior to the outbreak, nor was the diagnosis entertained in the initial cases. There was no undue apprehension about poliomyelitis among this hospital staff, but rather about infectious mononucleosis which was the early diagnosis. In spite of this the course of the disease and the type of neurological involvement was similar to that found in Los Angeles. In the Coventry outbreak six of the twelve patients had been nursing poliomyelitis cases for several years, and it is difficult to imagine why such experienced persons should suddenly manifest a hysterical reaction to the

fear of this disease. In the Middlesex Hospital, Berlin and Bethesda cases there was no known contact with poliomyelitis and, in the early cases at least, no reason for anxiety about it in the communities concerned.

The mental symptoms which are a constant feature of all the outbreaks are not typical of hysteria. Disorders of consciousness and convulsions such as may be seen in hysteria have been extremely rare. A single grand mal seizure was reported in a small child in Alaska. Shallowness of affect and "belle indifference" have not been seen. On the contrary, depression and undue emotional lability have been the rule. In the acute stage, terrifying dreams, panic states, uncontrollable weeping and hypersomnia occur. In the convalescent stage the prominent features are impairment of memory, difficulty in concentration and depression. These symptoms are more consistent with cerebral damage than with hysteria. Many years ago Von Economo [*55*] stressed the ease with which the mental symptoms of encephalitis may be confused with those of psychoneurosis. The slight lymphocytosis in the cerebrospinal fluid in two outbreaks [*6,17*] which shared many other features with the remainder, and the presence of a characteristic electromyogram in cases from three separate localities, are further strong arguments in favor of an organic etiology.

Final points against mass hysteria as a major factor in the syndrome are the consistency of the course of the illness, and the similarities in the symptoms described, in spite of a wide variation in the types of community affected, from hospital staffs on the one hand to semi-rural and urban populations on the other. The fact remains that in sporadic cases the illness may be extremely difficult to differentiate from hysteria and other types of psychoneurosis. [*31*]. The diagnosis should therefore be reserved, in isolated instances, for patients with evidence of acute damage to the brain or cord, including the characteristic paresis. If not, the syndrome will become a convenient dumping ground for nonspecific illnesses characterized by fluctuating aches and pains, fatigue and depression.

The Homogeneity of the Material. The clinical and epidemiologic evidence suggests that the fourteen outbreaks described in this review have not been due to any known neurotropic infection. The virologic evidence supports this contention so far as it goes, but it is incomplete. Thus poliomyelitis and Coxsackie virus were not formally ruled out in four outbreaks, and Echo viruses were not excluded in nine. It might be argued that at least some of the apparent clinical similarities are due to unconscious bias or undue emphasis on the part of observers familiar with the features of previous epidemics. Such bias cannot have contributed towards the striking reported similarities between the Los Angeles and Royal Free Hospital outbreaks [*5,12*] because Gilliam's paper was unknown to the British authors. These similarities are even more impressive when it is appreciated that bias was probably operating in opposite directions. In the Los Angeles outbreak the initial diagnosis was poliomyelitis, and the patients were cared for by orthopedists; in the Royal Free Hospital cases the initial diagnosis was infectious mononucleosis, and patients were treated by internists and neurologists. Further independent evidence is supplied by the Copenhagen cases. Fog's paper [*9*] was not known to the authors of the later Middlesex, Durban, and Royal Free Hospital reports, although once again they share many common features. It seems therefore that the syndrome is not a self-perpetuating medical artefact.

There are also important differences between the outbreaks. The paralysis rate varies from 10 per cent in the Punta Gorda outbreak to 80 per cent in the Los Angeles cases. The Los Angeles, Middlesex, Durban and Royal Free Hospital epidemics differ quantitatively from the remainder in regard to the frequency of neurological signs (other than paresis), notably cranial nerve lesions, hyperpathia, and retention of urine. They share with the Copenhagen cases a high incidence of paresthesias. On the other hand the Royal Free Hospital epidemics stand apart from the remainder because of the very high incidence of lymphadenopathy, which was otherwise limited to a few cases in the New York State, Middlesex [*8(c)*] and Durban outbreaks. The Iceland and Alaska epidemics differ from the rest in that a slight lymphocytosis in the cerebrospinal fluid was the rule rather than the exception. The length of the illness and the incidence of subacute and chronic cases have also varied.

Two outbreaks in particular stand apart in several important respects from the rest and it is debatable whether or not they should be classified with them. In the small Berlin outbreak [*15*] the illness was brief, sensory symptoms and signs were absent, and there were no sequelae or

chronic cases. A leukocytosis in the peripheral blood was another distinguishing feature. The onset was in November, later than in any other outbreak in the Northern Hemisphere. The outbreak at Punta Gorda [*16*] also began at an unusual time of the year (February). The onset of symptoms was insidious in all cases. Most of the cases were diagnosed on the basis of a house to house survey, presumably by retrospective questioning. Paresis was exceptional, and other objective evidence of disease of the nervous system was extremely uncommon.

In mild cases, when paresis and other signs of neurological involvement are absent, the illness has few differences in its early stages from many short-lived infections characterized by headache and generalized aches. Even in these patients, however, the degree of malaise and the severity of the pains are disproportionate to the disturbance of temperature and pulse. In the convalescent stage in such cases the easy fatiguability, the aches and pains, and the emotional disturbances without definite physical signs lead to difficulty in differentiation from psychoneurosis. Indeed, in the absence of an epidemic such a differentiation may be impossible.

In its epidemic form the illness is distinctive and therefore has a rightful place in medical literature as a clinical entity. Its epidemiological features suggest that it may be an infection. However, in the absence of any pathological evidence it remains uncertain whether it is due to a single agent or to a group of related agents.

As far as sporadic cases are concerned the diagnosis can be made with a degree of certainty only in cases which show all, or nearly all, the characteristics herein described, including paresis and some other objective evidence of neurological involvement which cannot be simulated. Negative virologic studies are also desirable. The diagnosis of less severe sporadic cases must await further knowledge of the pathology and the development of an objective laboratory test. Although further work is required before the electromyographic changes can be regarded as diagnostic, they may provide objective evidence of disease when this is otherwise lacking.

Treatment. No specific treatment is known to affect the course of the disease. Antibiotics were tried in the early stages of the Bethesda outbreak, when the diagnosis was uncertain, and in those patients in the Royal Free Hospital who had complicating intercurrent bacterial infections. No beneficial effect on the basic disease was observed. Steroid therapy has not been tried.

The importance of rest, as early in the disease as possible, and as absolute as practicable, is stressed by many authors [*5,12,15,18,19*]. Paretic limbs should be immobilized in the correct posture. Local heat may be used to abate pain and spasm. The association of premature rehabilitation with relapse is well described [*5,12,18,19*] and it is probable that bedrest should be maintained for some time after the disappearance of symptoms.

Symptomatic treatment is important in this painful and protracted disorder. Muscle relaxants such as meprobamate* have been tried [*12,15,17*] and have relieved muscle pain and tenderness in some cases. The sedative action may also be of value [*17*].

In a few cases full doses of narcotics may be necessary to control pain [*5,8,12*].

Complications should be treated as they arise. Retention of urine can usually be controlled by parasympathomimetic drugs such as carbachol [*12*] but occasionally catheterization or even tidal drainage will become necessary [*8,30*]. In rare instances of bulbar palsy, tube feeding has been necessary [*12*]. An artificial respirator has been required for a short time in three cases [*5,8*]. Shock treatment for severe depression was required in three of the Royal Free Hospital patients [*12*].

In the subacute and chronic stages constant encouragement and support is essential. The patient may be reassured that the trend is toward improvement and final recovery. Rehabilitation should be conservative, and return to work gradual.

NOMENCLATURE

The wisdom of naming a disorder, the nature of which cannot at present be proved, and which may be due to more than one agent, is debatable. That there are successful precedents is shown by the history of epidemic pleurodynia [*24,25,50*] and herpangina [*4,61*], both of which have subsequently proved to be virologic entities. In view of the widespread agreement that the illness described here is clinically recognizable in its own right, at least in severe cases [*15,17,22,31,46*], various authors have been of the opinion that a name is necessary for reference purposes. Un-

* Miltown (Wallace Laboratories, New Brunswick, New Jersey).

fortunately there has been no agreement as to what this name should be. White and Burtch [*14*] suggested "Iceland disease." This has the disadvantage of all eponyms that it gives no inkling to the uninformed of the nature of the disorder. It is also incorrect on historical grounds as the Los Angeles outbreak described by Gilliam is the original account in the literature. The same disadvantages (with the added difficulty of pronunciation) apply to "Akureyri disease" which is preferred by Sigurdsson and Gudmundsson [*21*].

The first attempt at a descriptive name was made by Fog [*9*] who suggested "neuritis vegetativa" in the belief that the autonomic nervous system bore the brunt of the damage. A further suggestion was made in an editorial in the *Lancet* in 1956 [*22*]. It was hoped that the term "benign myalgic encephalomyelitis" would emphasize the absent mortality, the severe muscular pains, the evidence of parenchymal damage to the nervous system, and the presumed inflammatory nature of the disorder. This term has been adopted by Galpine and Brady [*32*] and Deisher [*17*] in subsequent articles. It has also been criticized by Sigurdsson [*62*] and the staff of the Royal Free Hospital [*12,27*]. Sigurdsson objects that the disease is not always benign, not invariably myalgic, and possibly never encephalomyelitic. Benignity is relative; it seems that "benign" is justified by the fact that there is no other recorded infective disease of the central nervous system without mortality. As various authors have stressed [*5,8,12*], the pain in this disease, although not invariably present, may be devastating, and is perhaps the feature which impresses itself most forcefully on the observer. As far as the final term is concerned, the clinical impression that the lesion is central rather than peripheral is supported by the electromyogram. In our present state of ignorance "encephalomyelitis" seems preferable to "encephalopathy" because it conveys the suggestion that the disease is infective in origin, which is almost certainly the case.

In the Royal Free Hospital report it is pointed out that the name fails to describe the involvement of the lymph nodes and liver. As the author has indicated elsewhere [*63*], a fully descriptive name such as "benign ameningitic myalgic lymphoreticular encephalomyelopathy" is impracticable. Shelokov et al. [*15*] and Poskanzer et al. [*16*] have coined the phrase "epidemic neuromyasthenia." The first term is misleading because it suggests that the disorder is confined to epidemics; the second (translated nerve-muscle-weakness) is either meaningless or, if it means anything, suggests a disorder of the muscle end-plate, which is contrary to the electromyographic evidence. The verbal similarity with "neurasthenia" (i.e., psychoneurosis) is particularly unfortunate.

It is unlikely that an adequate term will be found until fresh evidence is available. In the meantime "benign myalgic encephalomyelitis" may act provisionally as a rallying point in the current list of medical literature for patients with the clinical features already described.

SUMMARY AND CONCLUSIONS

Fourteen outbreaks of a paralytic illness of world-wide distribution are described. Twelve of these have so many epidemiologic and clinical features in common that there is a prima facie case for a single or related group of causative agents.

The epidemiologic features are a high attack rate as compared with poliomyelitis, a predelection for residential communities, a higher attack rate in women than in men, a tendency to occur more commonly in young adults, and the commencement of most outbreaks in the summer months. The evidence is consistent with the hypothesis that the disorder is an infection which is spread by personal contact.

The fact that hospital staffs, particularly nurses, have borne the brunt of seven outbreaks suggests an occupational hazard. An alternative explanation is that the unusual nature of the illness has been noted in such persons because of a higher standard of diagnostic skill at their disposal than is available to the members of other residential communities.

Severely affected patients show a characteristic clinical picture. After an acute or subacute onset with headache, symptoms of a gastrointestinal or upper respiratory upset, muscular pains and low or absent fever, an unusual type of paresis develops which is rarely associated with the classic signs of lower motor neurone or pyramidal tract involvement. This is often accompanied by paresthesias, sometimes by sensory loss, and occasionally by painful muscular spasms, myoclonus or other types of involuntary movement. As the paresis recovers a curious jerky muscular contraction on volition has been noted in some instances. Involvement of the cranial nerves and the bladder may occur.

Convalescence has been prolonged by fatigue and recurring myalgia but recovery has usually been complete within three months. In a proportion which varies from outbreak to outbreak a well defined state of chronic ill health has developed, characterized by fluctuating myalgia and paresis, partial remissions and exacerbations, and depression, emotional lability and lack of concentration. The major differences within the group of outbreaks lie in the incidence of lymphadenopathy, paresis, and mild lymphocytosis in the cerebrospinal fluid.

Clinical laboratory studies have on the whole proved unhelpful. With the exception of two outbreaks in which a mild lymphocytosis was found, the cerebrospinal fluid has been normal in 95 per cent of cases investigated. An unusual electromyogram has been found in two outbreaks and in some sporadic cases.

No deaths directly attributable to the disease have occurred and the pathology remains unknown. In spite of the widest investigations, no known bacterial or viral pathogen has been incriminated. In particular, there is no evidence that the poliomyelitis, Coxsackie or Echo groups of viruses have been responsible.

Evidence is adduced to show that the outbreaks can be distinguished on clinical grounds from poliomyelitis, encephalitis lethargica, the arthropod-borne encephalitides, epidemic myalgia and infectious mononucleosis. The disorder is not a manifestation of mass hysteria.

It is concluded that the disease is recognizable in its epidemic form on clinical and epidemiologic grounds and therefore may properly be considered a clinical entity. In its sporadic form, which is now well documented, the diagnosis should be reserved at present for severe cases with definite neurological signs including paresis and the characteristic fluctuating course. The disease is probably due to infection by an unknown agent or group of related agents.

The problems of nomenclature and treatment are also discussed.

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Seminar on Connective Tissue

Serum Responses in Rheumatoid Arthritis*

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A MORE complete understanding of the peculiar serological reactions that occur in patients with rheumatoid arthritis has developed during the past decade. This has made available new information, the proper interpretation of which may well be a key factor leading to an understanding of the origin of the disease. As is inevitably so, this development of knowledge has not been isolated. There have been parallel advances on other investigative fronts and these have provided a substantial framework on which interpretation of the rheumatoid agglutination reactions can be cast. These advances include an improved understanding of the L.E. phenomenon in lupus erythematosus [*1–3*]; the experimental production of autoimmune disease [*4–6*]; the clinical identification of cases in which autoimmunity is implicated [*6–10*]; and new developments in thought and investigative effort on immunological tolerance and mechanisms of antibody formation [*11,12*].

In the sections to follow an attempt will be made to define what is known of the rheumatoid agglutinating factor [*13–16*]. Its proper setting with respect to other disease phenomena and to certain established patterns of biological responsiveness will be sought. Some lines for further investigation will be indicated.

PATHOLOGICAL CONSIDERATIONS

Rheumatoid arthritis is an inflammatory process of subacute or chronic nature, often vividly expressed in the hands, and characterized by swelling, pain, limitation of motion and slight warmth over the affected areas. Microscopic examination of the joints reveals a synovitis with cartilaginous changes secondary to the synovial reaction. In non-articular areas one may find granulomas, i.e., the rheumatoid subcutaneous nodule, which are characterized in the advanced form by palisading mononuclear cells contiguous on one side to fibrinoid necrosis, and on the other to an arteritic granulation. Sokoloff and co-workers [*17*] have emphasized the multicentric nature of this lesion and have pointed out that the fibrinoid appears very early on the periphery of a central granulation. Their concept that the lesion is centrifugal in nature, the zone necrosis being peripheral to the supposed site of origin of the lesion, is particularly intriguing. This suggested to them that the tissue reaction is mediated by a toxic substance diffusing out into the tissue from the intravascular space.

The recognition of fibrinoid alteration of the connective tissues as a prominent feature of rheumatoid disease has prompted the thought that the primary defect of the disease may lie within the connective tissues, the inflammatory features occurring as secondary phenomena. The converse can also be considered. The connective tissue may be involved secondarily, merely because the fiber-gel matrix which constitutes it is the necessary scaffolding upon which any primary leukocytic inflammatory infiltration develops. It is now recognized that fibrinoid contains fibrinogen and gamma globulin [*18,19*], both presumably of intravascular origin. There is no unusual amount of hydroxyproline in the lesion [*20*] or in the urine [*21*] to support the concept that collagen is being rapidly broken down. Normal and inflammatory leukocytes, on the other hand, contain an enzyme which is capable of depolymerizing normal tissue mucopolysaccharides [*22*]. Thus there is inherent in a

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leukocytic infiltration the capacity for inducing secondary change in the underlying connective tissues. Rheumatoid arthritis may therefore be considered primarily as a diffuse inflammatory disease, and not only the connective tissue changes but also the serological abnormalities may stem from this.

RHEUMATOID FACTOR

Sensitized Cell Agglutination Reactions. The ability of the serums of a large proportion of patients with rheumatoid arthritis to give peculiar agglutination reactions in high titer was first recognized in this country by Cecil and collaborators [*13*], who were interested in the possible relationship of the streptococcus to the disease. It was soon demonstrated [*23*], however, that not only the streptococcus but also rough forms of pneumococci and certain strains of staphylococci could be agglutinated in high titer by these serums. When sheep cells sensitized with subagglutinating doses of rabbit antisheep cell antibody also demonstrated this phenomenon [*15*], impetus was given to the belief that the rheumatoid factor is a non-specific material, perhaps much like serum complement [*23,24*]. However, several workers [*25–27*] investigated this possibility and showed that the rheumatoid factor cannot be identical with hemolytic serum complement, with one of its components, or with properdin [*26,27*]. Other possibilities remain. Rheumatoid agglutination may represent some other complement-like serum activity, e.g., conglutinin [*28*]. It may depend upon some completely non-immunological protein-protein interaction [*29*]. It may be an expression of autoimmunization, with the development of antibody against gamma globulin [*30–34*].

The sensitized sheep cell system (SSC) has been one of the widely used methods for demonstrating the rheumatoid agglutinating factor [*14,15*]. It has been adequately shown [*16,30–34*] that the reaction in this system is between the rheumatoid factor and the coating material on the sheep cell. Human red cells, guinea pig cells, or probably any type of cells can be substituted for the sheep red cells, so long as the cells are coated with an appropriate amount of rabbit antibody against them [*16*]. The antibody is used in a concentration which is itself insufficient to agglutinate the cell, but which in the presence of serums from patients with rheumatoid arthritis provides strong agglutination. When the sensitized sheep cell system is used, heterophil antibody must be absorbed from the rheumatoid serum prior to the test, to prevent agglutination by the heterophil antibody.

TABLE 1
UNUSUAL SERUMS AMONG 140 POSITIVE TESTS

Patient	Diagnosis	Agglutination Titers		
		F II	SHC	SSC
A. C.	Rheumatoid arthritis	2048	256	0
M. T.	Rheumatoid arthritis	512	64	0
V. C.	Rheumatoid arthritis	8192	512	0
D. E.	Rheumatoid arthritis	2048	128	0
E. G.	Rheumatoid arthritis	512	32	0
P. L.	Rheumatoid arthritis	1024	128	0
L. P.	Rheumatoid arthritis	1024	128	0
L. V.	Rheumatoid arthritis	256	64	0
W. W.	Rheumatoid arthritis	4096	32	0
E. M.	Rheumatoid arthritis	4096	8	128
N. V.	Rheumatoid arthritis	1024	0	128
R. W.	Rheumatoid arthritis	512	0	256
A. H.	Lupus erythematosus	>8192	0	256
L. H.	Polyarteritis	0	256	0

Cells have been coated with human gamma globulin by two mechanisms, and each has been very useful in detecting the rheumatoid factor. Sheep or human red cells can be gently treated with tannic acid in such manner that the cell surface non-specifically binds proteins to it [*35,36*]. Cells coated in this manner with gamma globulin (fraction II) provide the so-called tanned cell system for demonstrating the rheumatoid factor [*30*]. This is also referred to as the "F II" test. A sensitized human cell system (SHC) [*37–39*] has been used extensively in our laboratory. It employs Rh positive human red cells coated with non-agglutinating anti-Rh antibody.

The important feature is that the rheumatoid factor interacts in all these tests with the coating material, not with the cell. The species difference in the coating materials, as will be discussed, provides significant differences in the results obtained.

It can be seen from Figures 1 and 2 and Table 1 that the F II test gives titers significantly higher than the other two systems (SSC and SHC). However, when the results of the F II tests were strongly positive those of the SSC and SHC tests were generally also strongly positive. Occasionally, there were striking elevations in the titer in the F II test when one of the other two was completely negative. (Table 1.) This was more com-

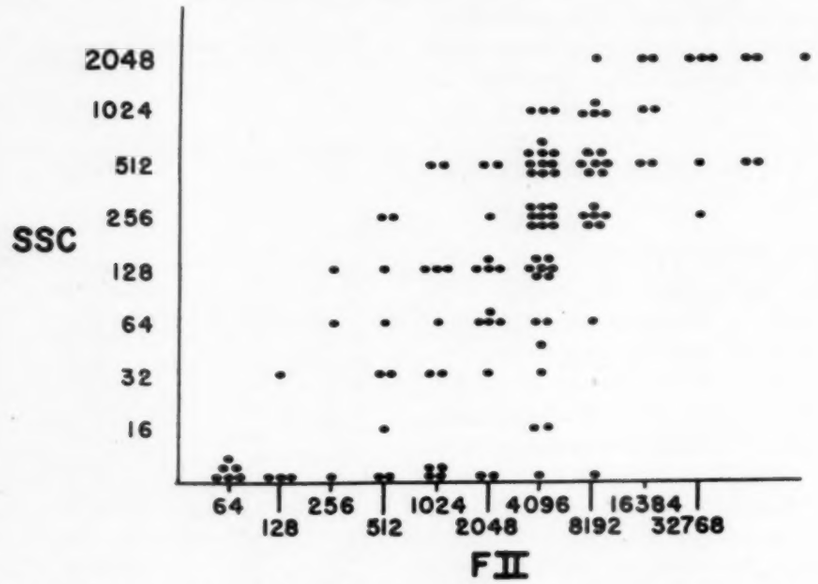

FIG. 1. Rheumatoid agglutination titers. Sensitized sheep cells (SSC) versus tanned sheep cells (F II).

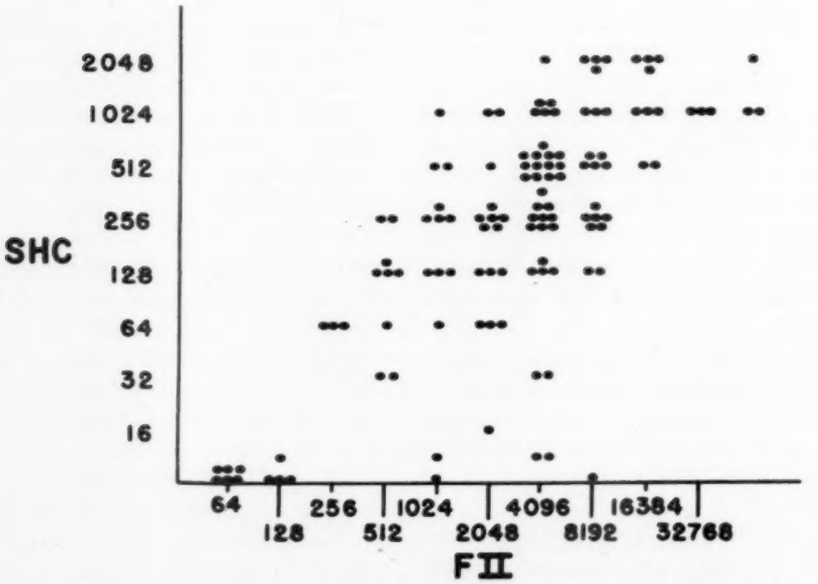

FIG. 2. Rheumatoid agglutination titers. Sensitized human cells (SHC) versus tanned sheep cells (F II).

monly seen in a comparison of the results of the F II and SSC tests, than of the F II and SHC tests. As a corollary, the SHC was twice as often significantly positive with a negative SSC, as was the SSC positive with a negative SHC. (Fig. 3.) The F II test was never negative in the presence of positive SSC or SHC tests, save a single instance (Table I), in a case of polyarteritis, when the SHC test was positive and the other two tests negative. The more readily demonstrated reactivity of the rheumatoid factor thus is with cells coated with human gamma globulin.

The Interaction with Gamma Globulin. A number of observations indicate that the rheumatoid factor reacts with gamma globulin rather than with some other substance in the material coating the sensitized cells. The most convincing of these experiments stems from Epstein, Johnson and Ragan's demonstration [*31*] of a precipitin reaction of rheumatoid factor with gamma

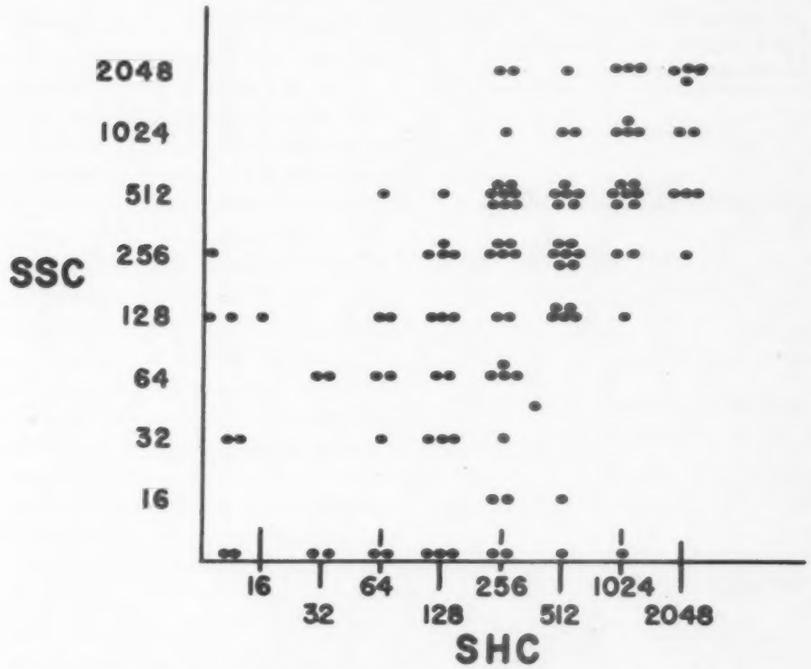

FIG. 3. Rheumatoid agglutination titers. Sensitized sheep cells (SSC) versus sensitized human cells (SHC).

globulin and from Franklin and his coworkers' [*40*] observations on the ultracentrifuge characteristics of the rheumatoid factor. The precipitation of rheumatoid factor from serum by gamma globulin has been shown [*40,41*] to be a function of aggregated gamma globulin molecules in the fraction II preparation used. Studies with labelled gamma globulin [*34*] show a changing ratio of added gamma globulin to rheumatoid factor in the precipitates at various points along the precipitin curve, suggesting multivalency for each of the reacting materials [*cf. 42*], and consistent with an antigen-antibody interaction.

Franklin, Holman, Muller-Eberhard and Kunkel's ultracentrifuge studies [*40*] on rheumatoid serums of very high titer indicated that the factor is a heavy protein with a sedimentation constant of 22 S. The heaviest human serum protein normally is a gamma globulin molecule with a sedimentation constant of 19 S and a molecular weight around 900,000. A lighter gamma globulin which sediments at 7 S and has a molecular weight of 160,000 constitutes the usual type of immune globulin in fraction II. Franklin et al. have been able to demonstrate [*43*] that the 22 S component is a complex of 19 S and 7 S gamma globulins. They have separated the 19 S component from the 22 S complex by appropriate dissociation and isolation techniques and have been able to show that the specific agglutinating capacity is a property of the 19 S protein. The 7 S component is without activity. Ultracentrifugation can be applied only to protein solutions containing relatively large quantities of protein. Serum-agglutinating activity may be exhibited by very small quantities of material. Therefore it may not be possible to demonstrate a 22 S component in serums of low or medium agglutinating titer. Whether or not the rheumatoid factor is present always as a 22 S complex is not certain.

Systems used for detecting the rheumatoid factor all contain 7 S gamma globulin, either in aggregate form or attached to cells by antibody bond. (Table II.) Such gamma globulin has been referred to as "reactant" by Epstein and Ragan [*44*]. In positive tests the reactant must either displace 7 S molecules that are already present in the 22 S complex, or it must bind the rheumatoid factor at sites other than those occupied by 7 S in the complex. In a recent study with a high titer rheumatoid serum, Christian [*45*] has presented evidence that in the F II precipitin reaction aggregated gamma globulin displaces 7 S molecules from the 22 S complex.

Although the entire demonstrable serum content of rheumatoid factor can be brought down

TABLE II
REACTANT PREPARATIONS FOR DETECTING RHEUMATOID AGGLUTINATION

Test	Form of Reactant Gamma Globulin	Manner of Attachment of Reactant Gamma Globulin to Cell or Particle	References
F II agglutination	Aggregated human 7 S	Adsorption	[30,41]
SHC agglutination	Unaggregated human 7 S	Antibody bond	[37,39]
SSC agglutination	Unaggregated rabbit 19 S and (?) 7 S	Antibody bond	[14–16, 77,100] [42,117]
Bacterial agglutination	Unaggregated human 7 S (?)	Antibody bond	[13,16]
Latex flocculation	Aggregated human 7 S	Adsorption (?)	[64]
Bentonite flocculation	Aggregated human 7 S	Adsorption (?)	[68]
F II precipitin	Aggregated human 7 S	.....	[31,41]
Immune precipitate absorption	Precipitated rabbit antibody (7 S)	.....	[33,34]

in a precipitate by human gamma globulin, a different result is found with rabbit gamma globulin. Antigen-antibody precipitates prepared from rabbit antiserums have been used as a source of insoluble rabbit gamma globulin and allowed to react with rheumatoid factor [33]. Easily measured amounts of protein nitrogen are absorbed from rheumatoid serums by these precipitates, and complete removal of agglutinating activity in sheep cells sensitized with rabbit antibody (SSC) results. Although rheumatoid serums absorbed in this manner exhibit only slight reduction in ability to agglutinate cells coated with human gamma globulin (the F II and SHC tests), they provide significantly less precipitable material in the F II precipitin test.

Rabbit gamma globulin prepared by alcohol fractionation [53] also reacts with the rheumatoid factor. It completely inhibits the SSC agglutination reaction but has minimal inhibitor activity for SHC. Rabbit gamma globulin heated at 63°C. for ten minutes may produce a precipitin reaction with rheumatoid serum, with the loss of SSC activity from the serum supernatant.

This situation is very similar to that which occurs in immunological cross reactions [*cf.* 42,48]. Absorption of antibody to a given antigen with cross-reacting antigen removes from the solution only those antibody molecules having specificity for surface configurations common both to the original antigen and to the cross-reacting antigen. The antibody remaining in solution after absorption reacts only with the original antigen. The heterogeneity of antibody for a given antigen has long been known by such observations on cross reactivity. The specific steric pattern of any given antibody molecule is complementary to only a limited area on the surface of an antigen molecule. This area has been estimated by Haurowitz at only three to four amino acid residues [46], although other estimates are somewhat larger [*cf.* 47]. With eighteen or more different amino acids composing most proteins, and 500 to 1,000 amino acid radicals per molecule, it follows that there may be a considerable number of immunologically distinct surface configurations on any given antigen. That antibody should ever behave as a single substance is indicative only of the fact that the various distinct antigen configurations for which the individual antibody molecules have specificity are on a single antigen molecule. Demonstration of independent subgroups of antibody to homologous antigen has recently been made by LaPresle [49] with antigen fragments prepared by partial enzymatic digestion. With the digested material, three bands were demonstrable in agar diffusion analyses against antiserums which had provided only a single band with the undigested antigen.

Gamma Globulin Groups. It is well recognized that the gamma globulins constitute a class of proteins with a spectrum of physical properties characterized, for example, by a broad peak in electrophoresis. Globulins identifiable as gamma globulins by immunochemical analysis can be found even under the beta or alpha-2 globulin peaks [50]. Chromatographic [51] and end group analyses [52] provide further evidence of this diversity. Among a large series of human serums containing non-agglutinating anti-Rh antibody, there are some that do and some that do not coat Rh positive cells so as to provide a sensitized cell system (SHC) satisfactory for demonstrating the rheumatoid factor [38]. It is probable that this is due to differences in the type of gamma globulin carrying the anti-Rh specificity in the

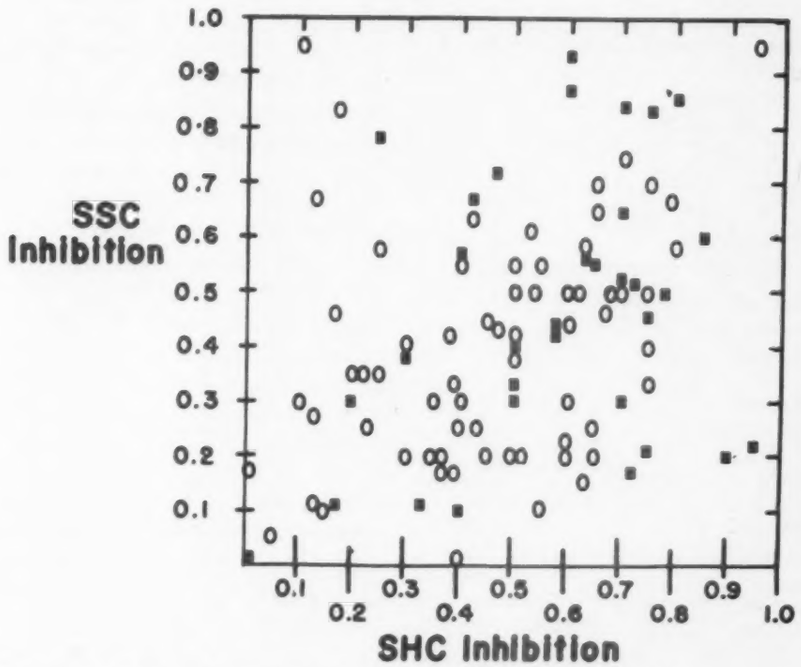

FIG. 4. Inhibition of sensitized sheep cell (SSC) and sensitized human cell (SHC) agglutination by non-rheumatoid (O) and non-agglutinating rheumatoid (■) serums. (See Table II for explanation of inhibition of rating.)

various individual anti-Rh serums used. There is good evidence in experimental animals [*42,51*] to indicate that in various individual serums a given antibody may be found among different gamma globulins, depending upon the circumstances of the immunization.

The importance of gamma globulin types in the rheumatoid system is also indicated by inhibition experiments [*39,53*]. If a dilution of serum containing the rheumatoid factor is mixed with undiluted fresh or inactivated normal human serum, the factor is prevented from reacting with the gamma globulin on sensitized cells subsequently added to the system. The relative capacities of various normal human serums to induce such inhibition can be titered. When this is done with a standard amount of rheumatoid factor and standard sensitized cells, considerable variation in different serums is noted. In both the SSC and SHC systems, some normal human serums inhibit agglutination to a very great degree, while other normal human serums fail to inhibit almost completely. (Fig. 4.) The lack of correlation between the two systems is striking; the possible meaning of this will be discussed subsequently. Agammaglobulinemia serums completely fail to inhibit [*53*].

Globulin preparations have been made from normal serums by sodium sulfate precipitation and by Cohn's method 10 [*54*] of alcohol precipitation of proteins. Serums with and without inhibitory activity were found to give globulin preparations with inhibitory activities corresponding to those of the parent serum, although somewhat less pronounced. (Tables III and IV.) There appeared to be important quantitative considerations, however, since the total amount of fraction II protein found per ml. of serum (Table IV) varied directly with the capacity of the original serum to inhibit. When the "non-inhibitor" fraction II preparations (Mo. and Di., Table IV), were concentrated to five and seven times their normal serum levels, respectively, they were then found to inhibit. Therefore it would seem possible that the Cohn method of separating fraction II may selectively isolate gamma globulins particularly capable of inhibition of rheumatoid factor. (It has been our experience that Cohn's method 10 for separating gamma globulins from human serum leaves some gamma globulin in fraction I + III.) We have also sometimes observed inhibition by proteins remaining in fraction I + III.

The observation by Mannik [*55*] that almost all fraction II preparations that he obtained were capable of inhibiting his rheumatoid ag-

TABLE III

INHIBITION OF STANDARD SHC AGGLUTINATION BY SERUMS AND SODIUM SULFATE FRACTIONS PREPARED FROM THE SERUMS

Patient	Preparations	SHC Agglutination in Serum Fraction Diluted 1:					Inhibition Rating*	Gamma Globulin† (%)
		2	4	8	16	32		
A. C.	Whole serum‡	−	−	−	+	++	0.76	20.7
	Unheated ppt.§	±	++	++	++±	++±	0.24	
	Heated‖ ppt.§	±	+	++	++±	++±	0.32	
G. F.	Whole serum‡	−	−	−	+	+±	0.80	19.3
	Unheated ppt.§	−	±	+±	++±	++±	0.44	
	Heated‖ ppt.§	−	−	++	++±	++±	0.44	
J. V.	Whole serum‡	±	+	+±	++	++	0.44	19.4
	Unheated ppt.§	++	++±	++±	++±	+++	0.00	
	Heated‖ ppt.§	++	++±	++±	++±	++±	0.04	
A. H.	Whole serum‡	+±	++	++±	++±	++±	0.09	18.0
	Unheated ppt.§	++±	++±	++±	++±	++±	0.00	
	Heated‖ ppt.§	++±	++±	++±	++±	+++	0.00	

* Inhibition rating: $1 - \frac{\text{Total plus values in the titration}}{5 \times \text{plus values of a control in saline } (+++)}$.

† γ-globulin in original serum protein, by paper electrophoresis.

‡ Inactivated at 56°C. for thirty minutes.

§ Globulins precipitated at half-saturated Na_2SO_4, redissolved and dialyzed against saline; final volume adjusted to that of original serum.

‖ 63°C. for ten minutes.

glutination reactions may have depended upon his utilizing fraction II gamma globulins in concentrations greater than in the serums whence they were obtained. It would seem that most if not all persons have (at least in some quantity) the type of gamma globulin required for interacting with and inhibiting the rheumatoid factor. Serums which give negative results in inhibition reactions would appear merely to have an insufficient amount of this particular gamma globulin to be demonstrable at their normal serum concentrations.

Grubb and Laurell [*39,56*] and others [*57,58*] have extensively studied the ability of various normal human serums to inhibit standard rheumatoid agglutination systems (SHC). On the basis of their results, Grubb and Laurell [*39*] described distinct serum groups, designating as gm. (a +) those which inhibit and as gm. (a −) those which fail to inhibit. Interestingly enough, extensive family and population studies [*39,56,58*] have demonstrated clear-cut genetic differences. In thirty-four families mating gm. (a −) × gm. (a −), for instance, Linnet-Jepsen et al. [*58*] found no one with gm. (a +) among ninety-three children, while the control population exhibited 45 per cent gm. (a +). Among sixty-eight pairs of identical twins, all exhibited the same gm. grouping; among fifty-one pairs of non-identical twins there were eighteen instances of differing groups, corresponding closely to an expected fifteen, provided the gm. phenotype was due to a single autosomal gene capable of existing in the heterozygous state [*58*].

The apparently limited ability of some types of gamma globulins to inhibit the rheumatoid agglutination reaction brings up certain further points of interest with regard to the rheumatoid patient's gamma globulin type. Persons with rheumatoid arthritis appear to be of both gm. (a +) and gm. (a −) types, as is indicated by the finding that among rheumatoid patients with negative agglutination reactions there is the same spectrum of inhibitory activities as among normal persons [*53*]. (Fig. 4.)* Since rheumatoid

* By direct comparison, the anti-Rh serum used in the SHC test of our laboratory provides for much stronger agglutination by rheumatoid serums than does the

agglutinating serums may or may not have prozones, it has been supposed [*59*] that this may reflect gm.a grouping. Those serums without prozones and with vigorous agglutination appear to be gm. (a −). Those that seem to be gm. (a +), although having titers of activity comparable to those among the gm. (a −) group, have prozones in which the agglutination is completely inhibited at high serum concentrations, and become stronger as the serum is diluted in the titration. Partition of serums through membranes of graded porosity, so as to segregate selectively the rheumatoid factor above the filter and allow uncombined gamma globulin to pass through to the filtrate in the bottom, allows examination of gamma globulins largely freed of the rheumatoid factor [*60*]. Those rheumatoid serums which give no prozone effects provide filtrates which are relatively inactive as inhibitors of a standard system, while rheumatoid serums which originally have strong prozones provide filtrates with strong inhibitory capacity [*60*].

The agglutinating activity of the factor remaining on top appears to be less discriminate than the original serum, with respect to ability to agglutinate cells sensitized with various anti-Rh serums [*38*]. This implies that the selective ability of the rheumatoid factor to react with only one or another type of gamma globulin is not absolute. Further quantitative evaluation of this effect will be needed to establish to what extent agglutination of sensitized human cells by rheumatoid factor is determined by the niceness of "fit" of the factor with the sensitizing antibody on the cell and to what extent it is determined by the quality or quantity of free gamma globulin in serum blocking access of the factor to the sensitizing antibody.

The observation that occasional serums react well in the SSC system and poorly or not at all in the SHC system (Fig. 3 and Table I) also needs explanation. It would seem possible that only certain human gamma globulin molecules have surface configurations like those found in rabbit gamma globulins and that this configuration is poorly represented among the gamma

TABLE IV

INHIBITION OF STANDARD SHC AGGLUTINATION BY SERUMS AND BY ALCOHOL FRACTIONS PREPARED FROM THE SERUMS

	Preparation	SHC Agglutination in Serum or Fraction Diluted 1:					F II* (mg. N/ml.)
		2	4	8	16	32	
An.	Whole Serum†	−‡	−	−	−	−	
		−‡	−	−	+	++	
	Unheated F II*	−	−	+	+±	++	2.3
	Heated§ F II*	−	+	+±	++	++	
		−	−	−	−	+	
Bo.	Whole Serum†	−	−	−	−	+	
		−	−	−	−	+	
	Unheated F II*	−	−	++	+±	++	1.4
	Heated§ F II*	−	±	++	++±	++±	
		−	−	−	−	±	
Mo.	Whole Serum†	−	+	++	++±	++±	
		++	++	++	++±	++±	
	Unheated F II*	++	++	++	++±	++±	0.4
	Heated§ F II*	++±	++±	++±	++±	++±	
		+±	+±	++	++±	++±	
Di.	Whole Serum†	±	±	+	++	++	
		±	+±	+±	++	++±	
	Unheated F II*	+±	+±	++	++±	++±	0.3
	Heated§ F II*	++	++	++±	++±	++±	
		+±	++	++±	++±	++±	

* Quantity of F II protein per ml. serum (Cohn 10, [*53*]).
† Inactivated at 56°c. for thirty minutes.
‡ Duplicated titrations on different days.
§ 63°c. for ten minutes.

globulins that make up the sensitizing antibodies in the SHC system. This interpretation would also account for the lack of correlation between inhibition of SSC and of SHC. (Fig. 4.) On the other hand one would expect to find all types of human gamma globulin molecules represented in the F II test, since thousands of individual blood plasmas contribute to any given pool of fraction II. This in part would account for results of the F II test being more often positive than either of the other two systems. The employment of newer electrophoretic and chromatographic techniques to separate gamma globulin types is needed to define these various factors more clearly.

The Role of Denaturation. A good deal of interest has been centered upon the effectiveness of heat and other forms of denaturation [*40,41*] in providing better gamma globulin reagents for rheumatoid precipitation, inhibition and agglutination reactions. This has suggested to some that the rheumatoid factor may be antibody primarily directed against denatured gamma globulin. The implication is that the factor is incapable, or less capable, of interacting with gamma globulin in an undenatured form. This

anti-Rh serums used by Grubb and Laurell for gm.a grouping. Inhibition of Grubb and Laurell's system by normal serums is therefore more easily accomplished than inhibition of the SHC system. No systematic study has been undertaken to determine whether other differences exist. The titer differences in Figure 4 are assumed to indicate differences analogous to gm.a grouping, but the exact relationship between the two systems cannot be stated with certainty.

perhaps might provide intellectual satisfaction to those who are attracted to the idea that the rheumatoid factor is an autoantibody to gamma globulin, but who nevertheless have had respect for the concept of *horror autotoxicus*. It is difficult, however, to accept the evidence that denaturation plays an essential role in the reactivity of the rheumatoid factor with gamma globulin. Since unmodified* plasma or serum can very effectively inhibit rheumatoid agglutination (Fig. 4), the assumption would necessarily follow that gamma globulin is denatured even in the simple drawing of venous blood and its coagulation at room temperature. It would seem quite likely that the role of heat and other denaturing agents is no more than that of a convenient laboratory artefact, which enhances the efficiency of the laboratory methods used to demonstrate the factor. In the precipitin reaction, for instance, mild denaturation might be regarded as providing an aggregated form of otherwise essentially undenatured gamma globulin, less soluble than the unaggregated form, and for this reason a better precipitating agent. Such material might also be expected to be a better inhibitor of agglutination because of the same greater insolubility, which would make it more effective in removing the rheumatoid factor from solution. The less soluble material would also more readily coat tanned cells [*cf. 41*], as has recently been inferred in studies of the ability of undenatured and denatured egg albumin to provide a tanned cell hemagglutination system for the detection of antibody in an egg albumin-anti-egg albumin system [*61*].

Thus the concept that denaturation of gamma globulin is essential in promoting the development of rheumatoid factor as antibody to the denatured form has as yet no solid basis in fact. The final answer to this question would be found if it were possible to measure the association constants (k), describing the interaction of the rheumatoid factor with the various forms of gamma globulin. That form of gamma globulin to which the rheumatoid factor less strongly binds would be considered less directly related to the factor. Present data do not provide this information, as the effects so far observed have been interpreted to be at least independent of binding energies.

Milgrom [*62*] has described a substance in occasional non-rheumatoid serums which reacts in much the same way as the rheumatoid factor. Unlike the rheumatoid agglutinating activity, however, this is not inhibited by normal gamma globulin, but only by eluates from sensitized red cells. Milgrom's factor has not been investigated as to whether or not it differentiates gamma globulin types. Milgrom regards his factor as antibody to altered gamma globulin.

Polypeptides and Sulfonamides. Heimer and associates [*63*] have recently re-examined the earlier reports that certain simple chemicals [*65*] and sulfonamides [*66*] can inhibit the rheumatoid reaction. Although it is true that the chemical nature of substances inhibiting rheumatoid agglutination reactions may give accurate information as to the stereochemical nature of the configurations for which the rheumatoid factor has primary specificity, this is true only if all possible non-steric factors can be reasonably ruled out. Thus Heimer's demonstration that if pH is carefully controlled, glycylglycine and sulfonamides have no ability whatsoever to inhibit the rheumatoid agglutination reaction permits us to disregard these reports.

Other Systems for Studying the Factor. Little attention has been given thus far to the mechanisms whereby rheumatoid arthritis serums can agglutinate substances such as bacteria [*13,23*], collodion particles [*67*], latex particles [*64*] and bentonite [*68*]. At the present time it is not possible to give a clear description of all the physicochemical factors responsible for these phenomena. However, some hints are available to us. In the case of bacteria, as has been shown by Wager [*16*], agglutinating activity is dependent upon coating of the bacteria by sensitizing antibody. In this respect bacterial agglutination can be regarded in the same class as the sensitized red cell agglutination reaction, and it is universally agreed that the bacterial agglutination titers of the arthritic patient do not measure an immunological response to the particular organism. It would appear [*16*] that rheumatoid patients have a normal amount of naturally acquired antibacterial antibody and that this provides for sensitization of the bacterium and thus an indicator system for the rheumatoid factor. This interpretation of the bacterial system is also consistent with the fractionation studies of Lamont-Havers [*69*].

* Although serums have been inactivated at 56°c. for the inhibition studies reported herein, this has been only to prevent lysis of the sensitized cells by complement. Such heat inactivation is not necessary for SHC inhibition, in which lysis by complement does not occur.

In the latex particle test, agglutination occurs in only a small number of rheumatoid serums unless gamma globulin aggregates are added to the system [*40,41,64*]. When agglutination occurs without the benefit of added gamma globulin, the rheumatoid factor is always present in extremely high titer and it would seem likely that the latex particle (and probably also the bentonite particle) merely acts as a nidus for the formation of precipitating aggregates of the rheumatoid complex, perhaps not much different from the action of dust particles in causing precipitation of salts from supersaturated solutions. The effectiveness of aggregated gamma globulin in bringing out positive reactions in serums containing lesser quantities of the factor complex probably depends on its binding with the factor, thus effectively building up the aggregate size until latex flocculation can occur.

The vagueness of our understanding of the physicochemical factors involved in the latex test, however, not only makes this interpretation rather uncertain but, more important, makes it difficult or impossible to be sure of the meaning of the effects of various polysaccharides on the system as reported by Singer [*26*] and by Gofton et al. [*70*]. Gofton's demonstration that chondroitin sulfate, heparin and hyaluronic acid can substitute for aggregated gamma globulin in the latex test may have no real biological meaning but may, as Gofton et al. point out, merely express the ability of these very negatively charged molecules to react non-specifically with gamma globulin and rheumatoid factor molecules which are relatively positively charged, thereby building up the aggregate size. The ability of hyaluronic acid to bind serum protein has been investigated directly by Meyer et al. [*71, cf. also 29,72*].

Singer's observations [*26*] that certain bacterial polysaccharides may inhibit latex agglutination and the observation by Brine, Wedgwood and Clark [*73*] that latex agglutination can also be inhibited by a heat-labile normal serum component possessing the properties of the second component of complement (C'2) seem likely to be based on similar non-specific interactions. Singer has cited evidence [*74*] that the normal serum latex test inhibitor is an alpha globulin.

Clinical Considerations. Although positive agglutination reactions can be demonstrated in a high proportion of patients with rheumatoid arthritis, they are not positive in all. In many studies of patients with rheumatoid arthritis the incidence of positivity is reported at the 70 to 80 per cent level [*64,75,76*]. In some it may even reach 90 per cent or more [*77–79*]. Even so, no laboratory yet has found a 100 per cent relationship between the presence or absence of the factor and the presence or absence of the disease. Thus it must be assumed that the disease may exist without recognizable amounts of the factor in the serum. In our own series, agglutination reactions were positive only in 67 per cent of the cases. (Table v.) It is particularly striking to note in Figures 1 to 3, however, that in relatively few instances agglutination occurred in low and intermediate titers. The tendency seems to be for the reactions to be very strong or to fail to occur altogether. In view of the known presence of inhibitor gamma globulin in many rheumatoid serums [*52*] (Fig. 4), and of the tendency for this globulin to cause prozones, it would seem that many weak agglutination reactions may be missed entirely because of their complete suppression by such gamma globulins. Attempts at separation of the rheumatoid factor from the other constituents of serum by fractionation procedures such as those of Ziff [*77*] and Svartz [*80*] are steps in the right direction. Both of these techniques need improvement, however, since both fail to separate the factor quantitatively. It is possible, therefore, that all rheumatoid patients may ultimately be shown to have the factor.

There has been an increasing tendency recently to use agglutination inhibition tech-

TABLE V
SPECIFICITY BY DISEASE

Disease	Serums (Total No.)	Positive Serums (Total No.)	Serums Positive by F II Only (No.)
Rheumatoid arthritis	169	113	6
Probable rheumatoid arthritis	14	6	2
Possible rheumatoid arthritis	39	5	3
Lupus erythematosus	10	4	1
Osteoarthritis	58	3	3
Gout	16	2	0
Miscellaneous non-arthritic diseases	113	7	4

niques to indicate the presence or absence of the factor, and by such means positive results have been recorded in over 95 per cent of rheumatoid serums [*77*]. Such tests make the assumption that all normal serums should have inhibition activity for the particular agglutination system used and that if this inhibitor activity is absent it is indicative of the presence of corresponding amounts of rheumatoid factor. There is no doubt that by such an approach a higher incidence of positive results in serums from rheumatoid patients is obtained, but it also has been reported [*81*] that this gives a higher incidence of false positive reactions in persons without rheumatoid arthritis. It has been our experience, furthermore, that individual normal human serums and also serums from rheumatoid patients with negative agglutination reactions vary markedly in inhibitor activity [*52*]. (Fig. 4.) Thus failure of inhibition may have either of two explanations, e.g., primary deficiency of inhibitor or, alternatively, its neutralization by the rheumatoid factor. Great care must therefore be exercised in interpreting agglutination-inhibition tests.

Positive agglutination reactions in very high titer occasionally occur in certain persons without rheumatoid arthritis. Such serums have been recognized particularly in sarcoidosis [*82*], syphilis [*83*] and liver disease [*82,84,85*]. The incidence of positive reactions in these disease groups is not nearly as great as in patients with rheumatoid arthritis, the figures being much closer to 10 to 15 per cent. Whether the agglutination reactions in liver disease are confined to patients with existing or pre-existing hepatitis is presently not clear, although early findings suggest this relationship [*84*]. The agglutinating activity in patients with sarcoidosis and syphilis has been detected almost exclusively by cells coated with human gamma globulin, that is, by the F II test or the SHC test. These serums generally do not agglutinate cells coated with a rabbit antibody, the SSC test.

Systemic lupus erythematosus and generalized scleroderma have been listed among the diseases giving rise to "false positive" reactions, reported at the 20 to 30 per cent level [*84,86*]. In our experience with lupus erythematosus this has been limited entirely to patients in whom the clinical picture of typical rheumatoid arthritis is present simultaneously. We have obtained no positive agglutination reactions in patients with scleroderma, but our series is small. Studies [*80*] implying that the agglutination factor in lupus serums is different from that in rheumatoid arthritis serums, because the activity in lupus serums often fails to precipitate when the serum is diluted in cold water, have uncertain meaning. First, the differentiation of the two clinical entities by this technique is by no means clear-cut. In our own experience, as already indicated, patients with lupus who have positive agglutination reactions of significant titer also have arthritis indistinguishable from rheumatoid arthritis. Secondly, it has been the experience of our laboratory that the rheumatoid factor activity in serums from patients with characteristic rheumatoid arthritis without any evidence of lupus may have significant solubility in cold water. It may be that the solubility differences that have been described [*77,80*] are much more the property of other serum proteins keeping the rheumatoid factor in solution than of the factor itself [*cf. 29*].

Important relationships have been recognized between the presence or absence of the rheumatoid factor and the objective clinical expression of the disease [*75–78,87,88*]. The factor often is absent early in the disease. It is found in a higher proportion of patients, and generally in higher titer, in those who have more advanced manifestations of the disease [*77,87*]. In advanced disease, the evidence suggests that the factor seldom disappears again. It is nevertheless interesting that in occasional instances patients may exhibit positive agglutination reactions at the time of their very first attack of clinically evident arthritis. de Forest [*88*] has given evidence that positive reactions may revert to negative in such patients, who subsequently prove also to have early remissive rheumatoid disease, as evidenced by striking improvement in clinical activity. The reversion of the reactions lagged significantly behind the change in the clinical status. Further, the development of a second attack of clinically evident disease occurred while the reaction was still negative, the reaction becoming positive again subsequently. Thus the positive rheumatoid agglutinations he reported followed in the wake of the disease.* It is interesting to draw a parallelism with the Wassermann antibody in syphilis, which disappears completely from the serum

* Other workers [*76,87*] have failed to find consistent changes in agglutinating activity after induced clinical remissions, although early remittent disease was not particularly studied. de Forest's data [*88*] need supplementing by others.

generally only in patients treated early with curative doses of penicillin [*89*]. When syphilis has been untreated over a long period of time, the Wassermann antibody commonly persists, even though the disease may be subsequently obliterated with antibiotic.

Although these observations imply a secondary role for the rheumatoid factor in rheumatoid disease, other observations suggest that its presence may modify the clinical expression of the disease. Subcutaneous nodules, for instance, are almost entirely limited to those patients whose serological reactions are positive [*87*]. Kellgren [*90*] has extended this observation, believing that he can distinguish clinically and with a high degree of certainty those patients whose serums have positive agglutination reactions from those whose serums are negative. He emphasizes the evidences of atrophy and degeneration of the cutaneous and subcutaneous tissues and the presence of signs and symptoms interpretable in terms of vascular disease. Franklin, Kunkel and Ward [*91*] have pointed to a high incidence of splenomegaly in a series of seven patients with especially high levels of rheumatoid-agglutinating activity. Duthie and co-workers [*92*] have noted that in patients with positive results to sensitized sheep cell tests functional capacity was significantly less and disease activity greater than in those with negative results. Finally, it has been the experience of our clinic [*93*] as well as that of others [*94,95*] that the development of the angiitis syndrome with peripheral neuropathy and gangrenous skin ulceration is particularly seen in patients with extremely high agglutinating titers.

Such correlative observations, however, do not establish cause-effect relationships. It remains true that patients with typical rheumatoid arthritis may have no demonstrable agglutinating factor. Further, an arthritis that in many respects resembles rheumatoid arthritis has been described in agammaglobulinemia. In these patients the results of tests for rheumatoid agglutination have regularly been negative [*53*]. If the rheumatoid factor in any way contributes to the production of arthritic disease, this contribution would seem at most to be slight.

Studies on Pathogenesis. Since the rheumatoid factor thus resembles a circulating antigen-antibody complex (*v. supra*) and since antigen-antibody complexes have a known relationship to serum disease and to the arteritis that is such a prominent feature of serum disease [*96*], it seemed important to determine experimentally whether or not the circulating rheumatoid factor complex has pathogenic significance. As rheumatoid arthritis has been recognized with certainty only in man, the experimental demonstration of the possible effect of the factor is likely to be demonstrated only in man. In a previous study Levinski and Lansbury [*97*] had failed to find evidence of transmissability of rheumatoid arthritis by joint fluid injections into volunteer recipients. In the absence, therefore, of an actively-infecting agent, any disease-producing effect of the factor should disappear in such time as the rheumatoid factor was metabolized and disappeared.

A single experiment [*98*] illustrates the pertinent findings. On transfusing high titer rheumatoid plasma into a normal volunteer recipient, the rheumatoid-agglutinating reaction was easily demonstrable in the recipient's serum, disappearing with a half-life that was in the vicinity of five to seven days. Repeated transfusions over a six-week period failed to reveal any evidence of an accelerated rate of disappearance of the factor, as one might have expected if the recipient had received the rheumatoid factor as a foreign antigenic material [*cf. 99*]. Nor, indeed, was there a faster rate of removal of the factor from the serum of the recipient on subsequent challenge some weeks after the initial studies. This was at a time when all activity from the previous transfusions had disappeared, and a time which would have corresponded to an anamnestic stimulation if the factor had acted as an antigen in this recipient.

At no time during the course of these transfusion studies did any evidence of arthritis or other illness develop in the recipient, even when minor trauma was inflicted in attempts to bring out subclinical phenomena. Other transfusion studies using white cells from rheumatoid patients, or white cells plus plasma containing high concentrations of rheumatoid factor, have yielded similar negative results. A single transfusion of rheumatoid plasma into another patient with rheumatoid arthritis yielded no evidence of exacerbation of activity. Thus, transfusion studies have failed to lend support to the concept that the rheumatoid factor complex can provoke disease.* However, these were

* M. V. Waller (personal communication) recently observed a newborn who was accidentally given a transfusion with a serum containing a high rheumatoid agglutinating titer. The infant suffered no deleterious

relatively short-term experiments, when compared with the months and years a rheumatoid subject is exposed to such a circulating complex. Furthermore, it is obvious that the titers of factor were not as high in these recipients as can be found in some patients with rheumatoid arthritis. The suggestions by Epstein [*95*] and Christian [*45*] that spontaneous precipitates developing from especially high titered serums may be significant factors in the development of the angiitis syndrome remains plausible. It is also conceivable that the isolated 19 S component of the complex could be far more pathogenic than the whole 22 S complex, which was probably the form in which the factor was transmitted in the transfusions described. Further studies will be required to clarify these points.

GENERAL DISCUSSION

The Non-antibody Hypothesis. The concept that the rheumatoid factor may be a normal protein present in very small amounts in perhaps all persons, but specifically elevated in the rheumatoid subject, is largely based upon the fact that low-agglutinating activity is often demonstrated in serums from healthy population groups [*100*]. This has made it necessary to define as "positive" only those serums with agglutination titers above a certain minimum serum dilution. Weak agglutination of sensitized cells in serum that has been diluted very little, however, need not necessarily represent the rheumatoid factor. Clearly, any charged particle, including red blood cells, suspended in a system of proteins and electrolytes such as represented by blood serum may be susceptible to numerous factors affecting the stability of the particles. The colloidal gold test on the spinal fluid in syphilis and in multiple sclerosis, for instance, depends upon the colloidal gold particles remaining stable in fluids low in protein, but becoming unstable with higher protein levels. Sensitized cells are no doubt somewhat susceptible to such non-specific protein effects. More important perhaps are complement [*42*] and so-called conglutinin [*28*] as further factors affecting an immunological system such as sensitized cells. Thus it would seem reasonable to suggest that only agglutination reactions performed in titer sufficient to "dilute out" such non-disease-specific factors be considered indicative of the rheumatoid factor. Potentiation of the SSC reaction by sheep serum [*100*] is probably on some such non-specific basis, and this aspect of rheumatoid agglutination reactions therefore is not more seriously considered in this review. It is worth pointing out that the flocculation tests for syphilis could probably be set at such a level of sensitivity that half the population would give positive reactions.

Since it is known that serum complement activity may be increased in disease, including rheumatoid arthritis [*101*], it is important to consider further the possibility that the rheumatoid factor represents one or more complement components. An early report [*24*] that the rheumatoid factor is identical with the fourth complement component (C′4) has not been substantiated in several laboratories [*25,26,29*]. Each complement component, and properdin, has been selectively eliminated from further serious consideration by specific inactivation experiments and also by the differential behavior between complement and rheumatoid factor with specific precipitates [*33*]. The recent demonstration [*73*] that a heat-labile serum substance with the properties of C′2 produces a prozone in the latex particle agglutination reaction probably should be interpreted in terms of "non-specific" serum protein effects with charged particles, as already pointed out.

The Antibody Hypothesis. It is difficult to take a firm position in opposition to the concept that rheumatoid factor, although not complement, is nevertheless a complement-like substance. There are, on the other hand, four main lines of thought that lead us away from this interpretation and towards the concept that it is antibody. First, the rheumatoid factor is a 19 S gamma globulin [*43*]. The 19 S gamma globulins constitute a group of proteins known [*42,43,102*] to carry with them antibody in the form of isoagglutinins, Wassermann antibody, cold agglutinin and agglutinating anti-Rh antibody, among others. Secondly, differential absorption studies with rabbit gamma globulin follow the immunochemical rules for the behavior of antibody with cross-reacting antigen [*34, cf. 42*]. Thirdly, like classic antibody to any given antigen, there is individual variation in the proportion of factor of a given serum capable of cross species reactivity. (Figs. 1 to 3, Table 1.) Even more, there is suggestive evidence that the rheumatoid

reaction. It is probable that such transfusions of rheumatoid agglutinating activity have often occurred incidentally in the course of therapeutic transfusions, but have gone undetected.

factor from one person may react preferentially with one portion of the spectrum of human gamma globulin, and that from another preferentially with another portion of the spectrum. (Table 1.) If the rheumatoid factor were a complement-like material or a "constitutive" or "natural" tissue constituent, one might expect it to have consistent reactivities with such standard reagents as are used in testing for it. The variability of these reactivities suggests that production of the factor is an adaptive phenomenon like that of antibody. The range of such individual variations would appear to be molded by the uniqueness of the individual [*103*] ability to respond to the presence of the provoking antigen.

The fourth argument in favor of interpretation of the rheumatoid factor as an antibody has no chemical basis but rather is an attempt to make sense from a biological point of view. The appearance of the rheumatoid factor in the serum of patients with arthritis is in no way a unique phenomenon. Patients with certain other diseases may exhibit the same or nearly the same phenomenon, lending credence to the belief that the appearance of the factor is a secondary or adaptive response to some other primary insult. More important, however, is the fact that rheumatoid serums may contain other substances that are reactive with the patients' own tissues. Nuclear staining of fixed tissues by rheumatoid serums has been seen by immunofluorescence [*104,105*], and positive L.E. reactions have been reported in 10 to 25 per cent of patients with disease clinically designated as rheumatoid arthritis [*106*]. Other diseases also are characterized by the development of serum factors reactive with the patient's own tissues. This has been described most extensively in hemolytic disease [*7–9*], in thyroid disease [*6,10*], in liver disease [*107*], and in lupus erythematosus [*108*]. In the present stage of knowledge, the least disordered hypothesis would place all these observations into a single type of biological response, autoantibody formation.

It is sometimes implied that autoantibody must necessarily be "autoaggressive." This is certainly not so. It has long been known that in experimentally induced encephalomyelitis autoantibodies to brain may develop [*109*], but that these fail to transfer this disease to normal animals by transfusion. Similarly, the rejection of homografts apparently is not effected by serum antibody [*110*], at least not by this alone. Quantitative as well as qualitative factors may be determinant in this respect [*111*]. It is clearly not necessary to envision a pathogenetic role for every demonstrable autoantibody.

Franklin et al. [*40*] have shown that six 7 S molecules are combined to form one 19 S molecule. This would indicate an immunological valency of six for the 19 S molecule, while classical antibody is known to have a valency of only two [*112*]. On the other hand, this valency for classical antibody has been established only with rabbit serums, in which the antibody was almost certainly a 7 S molecule. No data are available to indicate the valency of human 19 S antibodies.

Future Investigative Needs. Attempts should be made to determine whether or not the factor is synthesized in lymphoid tissue, as would be expected if the factor is antibody. Immunization studies are also desirable to indicate whether or not patients with rheumatoid arthritis have an abnormal capacity to form antibody. A change in serum level of the rheumatoid factor after repeated immunization with a given antigen may give some indication of whether the factor is produced because of stimulation by antigen-antibody complexes. Antibody in antigen-antibody complex may conceivably have enhanced antigenicity in a manner similar to that of heterophil hapten, when the hapten is injected together with pig serum into rabbits [*113*].

Arthritis that in several respects resembles rheumatoid arthritis has been described in animals [*114–116*]. A careful search should be made in these animals for serum substances like those found in arthritis in man to find out whether any of these animal diseases could be used as a laboratory model of rheumatoid arthritis.

A further study of the significance of gamma globulin groups in the development of the agglutinating factor is needed. Attempts to fractionate gamma globulin so as to isolate certain of the subcomponents, as detected by the rheumatoid-agglutinating system, may provide reagents in a sufficient degree of purity to allow more definitive study of the macromolecular reactions involved. With such reagents it should also be possible to pursue more precisely genetic relationships, not only in respect to gamma globulin groups, but also in respect to the presence or absence of the rheumatoid-agglutinating factor.

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Clinicopathologic Conference

Renal Failure in Primary Gout

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A THIRTY-SIX year old, white married man entered the hospital for the fifth time on September 14, 1958. He died on September 22, 1958.

The patient's first admission to Barnes Hospital was from June 15, 1952 to June 26, 1952. In 1942 the patient had been refused for military duty because of proteinuria. In 1946 he had noted the onset of painful swelling of the ankle joints. Some of these attacks were accompanied by fever. He was completely free of symptoms between attacks and for the first four to five years the only joints involved were the patient's ankles. In 1951 his arthritis became more extensive, involving at one time or another, the right side of the jaw, both knees, elbows, shoulders, fingers and both wrists. He entered another hospital where a diagnosis of rheumatoid arthritis was made and he was treated briefly with cortisone without dramatic improvement. The plasma uric acid level on that admission was 8.0 mg. per cent and the non-protein nitrogen 33 mg. per cent. Three days prior to the present admission he noted a recurrence of pain and tenderness in both knees, the right elbow, and the left small toe, wrist and hip. Fever, drenching night sweats and anorexia also occurred and the patient sought admission to the hospital.

There was no family history of arthritis. In the recent past the patient had noted a growth at the top of his left ear which broke down and exuded a white paste-like material.

Physical examination revealed a blood pressure of 138/88 mm. Hg. The ocular fundi were normal. The heart was not enlarged. There was redness, increased heat and swelling of the left hip, wrist and knee and of the right wrist. A fusiform swelling of the proximal interphalangeal joint of the right index finger was also noted.

Laboratory data were as follows: No hematologic abnormalities were noted. There was 1-plus proteinuria, with 3 to 4 casts per low power field in the urine sediment. A corrected sedimentation rate was 30 mm. per hour. The blood uric acid on two occasions was 10.8 mg. and 7.5 mg. per cent. The non-protein nitrogen was 32 mg. and 36 mg. per cent. Roentgenographic examination of the hands revealed soft tissue swelling of the right index finger. The chest film revealed no abnormalities. An electrocardiogram was normal. Phenolsulfonphthalein excretion was 20 per cent in fifteen minutes and 67 per cent in two hours. Urea clearance was recorded as 61 per cent of the average normal standard. Intravenous pyelograms were read as probably normal on the right; incomplete filling of the left renal pelvis. There was striking relief of symptoms with the oral administration of colchicine and he was discharged with instructions to follow a regimen consisting of a fluid intake of 4 L. per day; a low purine diet; Benemid,® 1 gm. a day; and colchicine, 0.5 mg. a day. He did well with this regimen until about 1955 when he again began to note frequent episodes of joint pain. He was followed up in the clinics periodically and uric acid levels were always 6 to 8 mg. per cent, even while he was taking Benemid.

The patient's second admission to the Barnes Hospital was from November 11, 1957 to November 27, 1957. One year prior to this admission, the patient's urine specimens had a specific gravity ranging between 1.007 to 1.010 with 1- to 2-plus proteinuria. The blood nonprotein nitrogen gradually rose to 67 mg. per cent in 1957. He was hospitalized on November 11, 1957 for renal evaluation.

Physical examination revealed a blood pressure of 198/115 mm. Hg. Grade 2 retinopathy was present. Cardiomegaly was noted. Fusiform

swelling of the proximal interphalangeal joints was observed, the right finger being more swollen than the left, and there was a swollen olecranon bursa on the right.

Laboratory data were as follows: Urine specific gravity was 1.006. There was 4-plus proteinuria but there were no abnormalities in the urine sediment. The packed red cell volume was 35 per cent. Stool guaiac was negative. The electrocardiogram and roentgenogram of the chest were within normal limits. The blood non-protein nitrogen on admission was 71 mg. per cent; the urea nitrogen, 51 mg. per cent. A week later blood non-protein nitrogen was 66 mg. per cent. Serum uric acid on admission was 5.7 mg. and repeat levels of 4.9 and 6.1 mg. per cent were obtained. Serum electrolytes, calcium, phosphorus, alkaline phosphatase, and cholesterol were all within normal limits. Several lupus erythematosus preparations were negative. Initial culture of a non-catheterized urine specimen revealed a moderate growth of white and yellow staphylococci, but repeated cultures thereafter revealed no growth. Prostatic fluid culture was negative. The urine specific gravity did not rise above 1.012 after water restriction. A twenty-four hour urine collection contained 3.4 gm. of protein. A phenolsulfonphthalein test showed 3 per cent of dye excreted after fifteen minutes; the urea clearance was 11 ml. per minute, and a creatinine clearance was 32 ml. per minute. After intravenous pyelograms demonstrated only faint bilateral excretion, a retrograde pyelogram was performed on the left (the side on which incomplete filling had been seen previously) but there was no evidence of calculi or obstruction.

During the course of hospitalization there were a number of exacerbations of acute arthritis, mostly of minor degree which responded to extra doses of colchicine. On one occasion it was necessary to administer phenylbutazone for the relief of symptoms. Sodium citrate therapy was begun in an effort to alkalize the urine. The administration of Benemid was discontinued and replaced with Bufferin,® in an amount equivalent to a daily dose of 4.2 gm. acetylsalicylic acid. Shortly before discharge, the spleen became palpable just below the left costal margin. The patient was discharged with instructions to take Bufferin, 14 tablets a day; and sodium citrate, 8 ml. three times a day. He did poorly after discharge and had many attacks of upper abdominal pain and frequent episodes of dizziness.

The patient's third admission to the Barnes Hospital was from February 18, 1958 to March 25, 1958. The patient was admitted for the third time on February 18, 1950 because of tarry stools for three days, and hematemesis on the day of admission.

Physical examination revealed a blood pressure of 220/130 mm. Hg; pulse, 92 per minute, and temperature, 37.2°c. There were blurred disc margins with a few round hemorrhages and waxy exudates bilaterally in the fundi. Cardiomegaly was again noted. A grade 2, harsh systolic murmur was audible at the aortic area and apex. A left inguinal hernia was present. There was no peripheral edema.

Laboratory data were as follows: Hemoglobin, 6.1 gm. per cent; hematocrit, 30 per cent; white blood cell count, 10,000 per cu. mm.; examination of the peripheral blood smear revealed no abnormalities. Two-plus proteinuria was present with occasional red blood cells and white blood cells in the urine sediment. No uric acid crystals were seen. The stool guaiac was strongly positive. Examination of blood indices revealed a mean corpuscular volume of 85.3, mean corpuscular hemoglobin of 23, and mean corpuscular hemoglobin concentration of 28. Roentgenographic examination of the gastrointestinal tract was interpreted as showing gastritis and duodenitis. The gastric contents were guaiac positive. The blood non-protein nitrogen was 182 mg. and the uric acid was 7.9 mg. per cent. Serum electrolytes were within normal limits. Daily excretion of urinary uric acid ranged between 300 and 800 mg.

The patient initially required 5 units of whole blood. Administration of salicylates was reinstituted with milk and alkali feedings, but bleeding recurred and 7 units of whole blood were required to maintain his hematocrit. One brief hypotensive episode was noted during this massive bleeding, but was corrected by rapid infusion of whole blood. Following this episode a diuresis developed of 5 to 6 L. per day. Excretion of sodium in the urine rose to 300 to 350 mEq. per L. per day and it became quite difficult to maintain the daily sodium requirements. It was thought that the patient might have had a mild acute tubular necrosis with subsequent diuresis. After the bleeding ceased, the hypertension was treated with Dibenzyline,® 10 mg. administered twice daily. He was also given colchicine, supplemental sodium chloride, sodium bicarbonate, and vitamins. At the time of discharge the hyper-

tensive changes in the fundi were markedly improved. (The twenty-four hour excretion of 17 ketosteroids was 6.2 mg.; the excretion of 17-hydroxycorticosteroids was 3.3 mg. per day.)

Following discharge, the urine output and daily excretion of urine sodium remained high. Over the next few weeks the sodium excretion for twenty-four hours slowly dropped to 100 mEq. per day.

The patient's fourth admission to the Barnes Hospital was from August 9, 1958 to August 30, 1958. In July 1958 weakness developed, and the patient had symptoms of congestive failure which were poorly controlled with digitalis therapy. He was admitted on August 9, 1958 with increasing edema and lethargy.

Physical examination revealed a blood pressure of 180/90 mm. Hg and respirations of 18 per minute. He appeared chronically ill with marked edema of the face and legs. Hemorrhages and exudates were present in both fundi. The left disc margin was blurred. No rales were noted. A grade 2 precordial systolic murmur was present. There was marked edema of the ankles.

Laboratory data were as follows: Hemoglobin was 6.1 gm. per cent with a hematocrit of 24 per cent. The urine contained 2-plus protein with 0 to 5 red blood cells and 0 to 2 white blood cells per high power field in the sediment. Serum sodium was 122 mEq. per L.; potassium, 3.9 mEq. per L., chloride, 77 mEq. per L.; CO_2 23 mEq. per L.; non-protein nitrogen, 135 mg. per cent. Uric acid was 11.8 mg.; calcium, 6.6 mg.; phosphorus, 12.5 mg. per cent; alkaline phosphatase, 2.7 Bodansky units. The serum albumin was 3.6 gm.; globulin, 1.5 gm. per cent. Urine culture was negative.

The hospital course was complicated by hyponatremia and an increasing weight while the patient maintained a large water intake; but when water was restricted, both the non-protein nitrogen and the serum sodium rose markedly. The patient continued to excrete approximately 240 mEq. per L. sodium and 100 mEq. per L. potassium per day. He was discharged on August 30, 1958 taking digitalis; Apresoline,® 50 mg. four times a day; Basalgel®; colchicine; and an 8 gm. salt diet.

The patient's final admission to the Barnes Hospital was from September 14, 1958 to September 22, 1958. Because of the development of marked orthopnea and pain in the lower left side of the chest he was hospitalized again on September 14, 1958. The additional family history was obtained that the patient's paternal grandfather had had rheumatism; his paternal uncle had been diagnosed as having gout in 1957; his father had had pain in the left great toe in 1958.

Physical examination revealed a blood pressure of 230/130 mm. Hg; pulse, 120 per minute; and temperature, 38°C. The patient had spasmodic muscle jerks and was acutely orthopneic. Bloody crusts were present in the nose. The fundi were described as a grade 4 retinopathy. Bubbling rales were present throughout the chest and respirations were rapid and shallow. A loud pericardial friction rub was present and there was a loud systolic murmur at the apex. Two-plus pretibial edema was noted.

Laboratory data were as follows: Hemoglobin, 5.7 gm. per cent; white blood cell count, 5,000 per cu. mm.; there was moderate hypochromia and anisocytosis with adequate platelets on examination of the peripheral blood smear. There was 4-plus proteinuria; 3 to 4 red blood cells and 4 to 5 white blood cells per high power field in the urine sediment. Roentgenograms of the chest demonstrated cardiomegaly and pulmonary congestion. An electrocardiogram was interpreted as showing sinus tachycardia. The non-protein nitrogen was 318 mg. per cent; plasma sodium, 138 mEq. per L.; potassium, 5.3 mEq. per L.; chloride, 101 mEq. per L. and CO_2, 14.6 mEq. per L.

The patient's hospital course was complicated by recurrent pulmonary edema, plasma potassium values ranging from 5.5 to 7.0 mEq. per L. and relatively poor urine output (usually less than 1,000 ml. per day). On September 19, 1958 necrotic lesions of the mouth developed. On September 22, 1958 he was hypotensive and shaking his head from side to side. He died a short time later.

CLINICAL DISCUSSION

DR. SOL SHERRY: This patient was noted to have proteinuria at the age of twenty significant enough to cause his rejection from military service. From age twenty-four to twenty-nine he had recurrent bouts of arthritis. These were at first limited to the ankles, but subsequently involved multiple joints. His first admission to the Barnes Hospital was at the age of thirty for arthritis, at which time the diagnosis of gout was made. The second admission to the Barnes Hospital, five years later, was for renal evaluation.

At that time he was found to have hypertension and fairly advanced renal insufficiency. His third admission to the Barnes Hospital was the following year for severe bleeding of the upper gastrointestinal tract which was attributed to salicylate therapy. A hypotensive episode and acute renal failure developed. He finally recovered, but he was left with a diuretic and natriuretic syndrome. Six months later, he was admitted for the fourth time with anasarca which was believed to be due to congestive heart failure and water overloading. He was noted to have severe hypertension and moderately advanced uremia. Two weeks later he was admitted for the fifth and final time with severe uremia, pericarditis, heart failure and a rapidly decreasing urinary output. He became semicomatose and died. Dr Humphrey, would you discuss the roentgenograms?

DR. HARVEY A. HUMPHREY: Roentgenograms were obtained on the first admission in 1952. Swelling was observed in the proximal interphalangeal joint of the right index finger. There was some edema around the left wrist and soft tissue swelling on the lateral aspects of the fifth digit on the left hand suggestive of tophi. Similar changes could also be seen on the right index finger. The bones were not demineralized or eroded. Intravenous pyelography showed good concentration of the dye although the kidneys appeared contracted. Oh the second hospital admission in 1957, renal function was markedly impaired as shown by the decreased concentration of dye being excreted bilaterally. The kidneys appeared somewhat smaller than on the first admission. No stones were evident. In 1958, at the time of the gastrointestinal bleeding, the mucosal folds in the stomach appeared thickened. There was evidence of a gastritis, a duodenitis and perhaps a duodenal ulcer. With regard to the cardiopulmonary changes, both the lungs and the heart were normal in 1952. On the second admission the aorta had become unduly prominent with evidence of hypertension. There was minimal ventricular enlargement. On the third admission, the heart was somewhat larger, the left ventricle was more prominent and pulmonary vascular congestion was evident bilaterally. On the fourth admission, the heart had increased further in size. There was evidence again of bilateral pulmonary congestion. On the final admission, there was progressive cardiac enlargement and evidence of pericardial effusion. The lungs had changed quite markedly, and could be described either as pulmonary edema or azotemic pneumonitis.

DR. SOL SHERRY: The body, in its continuing efforts to maintain a normal state or to repair previous injuries, frequently is faced with the problem of handling large insoluble aggregates, as for example, fibrin, fibrinoid, nucleoprotein and amyloid, which accumulate in the extracellular compartment, in the connective tissues, and commonly in the vascular bed itself. Occasionally the problem relates to simple compounds, which, because of their sparing solubility, tend to readily crystalize when increased amounts are present in the body fluids. In today's case, which exemplifies this latter problem, the culprit is uric acid. That our patient had primary gout seems well established. There was a positive family history of gout; there were typical acute attacks of joint distress; there was a good response to the administration of full doses of colchicine; and the serum uric acid was persistently elevated above 6 mg. per cent. Subcutaneous tophi were present and there was renal dysfunction. The sole criterion lacking, was evidence of bony tophi by roentgen examination, a finding not critical for the diagnosis. Primary gout is a hereditary disease and I shall generalize that all hereditary diseases have as their basis, a genetic abnormality. This genetic abnormality expresses itself as an altered metabolic pathway, or biochemical lesion. The biochemical lesion may then produce pathological lesions which express themselves as clinical syndromes. In gout, the genetic abnormality may be termed the gouty diathesis. The biochemical lesion is expressed as increased amounts of sparingly soluble urates throughout the extracellular compartment. The pathological lesions relate to the precipitation and deposition of urates in synovia, connective tissue, bone and renal tubules. Precipitation of urates in the synovia along with other important, but poorly understood factors, leads to acute gouty arthritis with its intercritical symptom-free periods. The deposition of urates in connective tissue and bone leads to chronic tophaceous gout. The deposition of urates in the renal tubules and renal parenchyma may lead to nephropathy. The progression of these aspects of gout, that is, arthritis, chronic tophaceous gout, and nephropathy are influenced by different factors, and as a result may be more or less important in any particular patient. It should also be remembered that although the arthritis is painful and the

tophi disfiguring, it is the nephropathy which is hazardous. Renal failure is a primary cause of death in gouty patients, irrespective of age, and an important cause of death prematurely. Chronic renal impairment may go hand in hand with advanced joint disease, or it may completely overshadow what appears to be a relatively minimal joint involvement. Let us begin our discussion with a consideration of the hereditary factors in gout. Dr. Daughaday, will you comment on this?

DR. WILLIAM DAUGHADAY: As you pointed out, it has long been known that gout runs in families. However, real progress in unraveling the heredity of gout dates from the recognition that hyperuricemia, independent of arthritis, occurs in about 25 per cent of the members of gouty families. I have selected a family tree of a particularly remarkable gouty family described by Gutman. In the first generation the father had gout. In the second generation the daughter had hyperuricemia and was unfortunate enough to marry a person with gout. Of their ten children, there were two with clinical gout; five with hyperuricemia; and, interestingly enough, two siblings escaped. Gutman would like to have us believe that the two parents in this generation were homozygous for the gouty gene.

How can we best explain the inheritance of gout? The predominance of the disease in men suggests the possibility that it is transmitted as a sex-linked recessive. There are many reasons for not believing this hypothesis, but I will not go into them, except to point out that a father can transmit the disease to a son.

The preferred explanation for inheritance of gout at the present time, is that it is transmitted by a dominant gene with incomplete penetrance, by which is meant that not all the individuals possessing the gene can be detected. The degree of penetrance depends to a great extent on the refinement of the method used to detect the character. If we recognize only clinical gout, this gene would be poorly penetrant. If we consider hyperuricemia, the penetrance would be ten times greater. If we had even a better biochemical test, we could perhaps recognize all carriers of the gene.

Given the hereditary diathesis, there are many factors which influence the expression of the abnormality. The sex of the individual is one such factor. Even in the absence of the gouty diathesis the mean uric acid level in males is about 0.8 mg. per 100 ml. of serum higher than in females. This difference occurs in gouty families as well and may predispose the male to clinical arthritis. Age is another factor that I should mention. It is rare for hyperuricemia to be established in males before puberty, suggesting that androgens take part in hyperuricemia. In women, hyperuricemia may be delayed until after the menopause. Gout is very rare in women prior to the menopause. Other genes may modify the expression of the gene for gout and there are some who suggest that the inheritance of gout is conferred by multiple factors.

I should mention that Smythe has calculated the approximate frequency of heterozygotes in the general population to be about 0.88 per cent. Another interesting speculation is that one of forty-four patients with gout is homozygous for the character. Perhaps the extreme severity of the disease in this particular individual may not be due to the fact that he is carrying one gene, but he may have a double dose.

DR. SHERRY: Does the fact that our patient's gout became evident at a very young age, imply a more severe genetic disturbance and in turn a more florid biochemical lesion?

DR. DAUGHADAY: Independent of the genetic analyses, gout occurring earlier has a more serious prognosis, but the suggestion is a reasonable one, that certain particularly severe cases are instances of true homozygotes.

DR. SHERRY: Dr. Recant, what is the current status of the biochemical lesion in gout?

DR. LILLIAN RECANT: The patient with gout usually has an elevated uric acid level. However, a direct relationship between this elevation of uric acid and the occurrence of acute gouty arthritis has not been established. In fact, injections of uric acid in gouty subjects cannot produce the acute attack of gout. Further, the administration of colchicine, an effective agent in the treatment of acute gouty arthritis, has thus far not been shown to influence the level of serum uric acid. We are left, then, with a chemical abnormality that is observed in patients with acute gout, but one not apparently related to the symptom complex. In chronic gout, however, there is a clear relationship between the pathologic condition and the accumulation of uric acid in the blood and the tissues.

Let us then consider the mechanisms by which uric acid may accumulate in the patient with gout. First, where does uric acid come from and what happens to it in the normal human subject? An exogenous source of purines may be found in

foods which are rich in nucleoprotein. These foods are converted to free purines in the body and as such serve as a source of uric acid. The body is also capable of synthesizing purine *de novo*, from small molecules such as glycine, formate, ribose, and carbon dioxide. In addition, the nucleoprotein constituents of the body, which are constantly turning over, also serve as a source of purine compounds. Finally, the body purines are converted to uric acid by a series of oxidative, enzymatic steps. Until recently, it was thought that the body would rid itself of uric acid only by the renal route. However, it has been shown recently that a small portion of uric acid is converted to urea and excreted as such. There has also been a report by Laster which indicates that human red blood cells contain a uric acid-ribose compound. In order to understand the accumulation of uric acid, one may postulate three mechanisms. First, an overproduction in which urate is formed more rapidly and in greater amounts than normal; second, a retention mechanism in which the kidney does not excrete the normal amount of urate; and third, a mechanism which would involve a decrease in the rate of breakdown of uric acid, such as a decrease in its dissipation to urea, and, perhaps, the uric acid-ribose compounds.

In the patient with primary gout, the excretion of uric acid is usually normal. It would be difficult, however, to demonstrate a slight decrease in excretion since so much of the urate is normally reabsorbed by the kidney. On the other hand, there are patients with gout who excrete more uric acid than normal subjects. With regard to the mechanism of overproduction of uric acid, the experiments of Wyngaarden, Stetten, Gutman and others, utilizing isotope-labeled precursors of uric acid, have indicated that in a small proportion of gouty subjects, there is indeed an increased formation of uric acid. However, recently, it has become clearer that this occurs only in a small number of subjects who are clinically indistinguishable from those who do not show this abnormality. One must conclude, then, that overproduction of urate does not occur in all gouty patients. There is one question, however, which concerns methodology here in these experiments and still leaves the question open. Can one accurately measure the rate of incorporation of isotope into urate in the face of a large pool of unlabelled uric acid, which would dilute out the newly synthesized uric acid? Finally let us consider the possibility of a decreased conversion of urate to other compounds. Laster has reported that in human subjects there are specific enzymes which are called uric acid-ribose phosphorylases, which convert uric acid-ribose, in the presence of inorganic phosphate, to uric acid and ribosephosphate. Interestingly enough, Laster has shown that this reaction can be inhibited *in vitro* by colchicine. I think it is too early to draw any conclusions from these data. However, I believe that these data open up new concepts in the understanding of urate accumulation and gout. There may be several types of primary gout, possibly with differing metabolic defects. Some may have overproduction of urate, while perhaps others may show decreased breakdown of urate or other alterations. Finally, the nature of the defect may relate to homozygous or heterozygous gouty states.

DR. SHERRY: Dr. Bricker, from time to time investigators have claimed that the primary defect in gout may really be in defective mechanisms for the handling of the uric acid by the kidney. I wonder whether you might briefly summarize for us what is known about the normal mechanism of uric acid excretion and whether or not there is any evidence to support the view that primary defects in renal mechanisms may be present in patients with gout?

DR. NEAL S. BRICKER: The concepts regarding the mechanism of the renal excretion of urate have varied considerably over the years and there is still no unanimity of opinion today. Perhaps the most widely accepted view, however, is as follows: Urate is very likely completely, or largely, filterable. This would then imply that the concentration of urate in the glomerular filtrate is virtually identical to that in the plasma. Hence the amount of urate entering the nephron is determined by the product of the glomerular filtration rate and the plasma urate level. As the tubular urine begins its course down the tubule, urate is reabsorbed. It is thought that this probably occurs in the proximal segment. The transport mechanism is active and, presumably enzymatically driven, and over 90 per cent of the filtered load of urate is ordinarily reabsorbed. The remainder is excreted into the urine.

When plasma urate levels are increased in normal subjects by infusion of urate, not only does the filtered load of urate increase, but also reabsorption, such that virtually all the increment in filtered urate is reabsorbed. Consequently, the amount of urate excreted does not

increase predictably. When plasma urate levels are increased above 12 to 15 mg. per cent in a subject with a normal filtration rate, a Tm for the urate mechanism can be demonstrated and above this point no further reabsorption occurs, despite additional elevation of the filtered load.

In the patient with gout and hyperuricemia, the filtered loads of urate are constantly high if the filtration rate is normal. When one plots the amount of urate absorbed against the amount filtered, and superimposes this plot on that of normal subjects receiving urate infusion, only one population emerges. Thus there is no detectable difference in uric acid reabsorption between the subject with gout and the subject without gout. One additional point might be made. There has been considerable speculation about the fact that urate might also be secreted by the tubular epithelial cells. If this is true, and it has not yet been demonstrated in man, many of our present concepts must undergo revision.

DR. SHERRY: Do you think it is possible that a defect in a urate secretory mechanism, if such normally exists, might be responsible for gout?

DR. BRICKER: If it could be established that all the filtered urate is reabsorbed in the proximal segment, and the total amount entering the urine is derived from tubular secretion, it is conceivable that a slight defect in the secretory mechanism over a period of months to years could account for the development and perpetuation of hyperuricemia.

DR. SHERRY: Dr. Kirk, several years ago you presented evidence demonstrating secretion of uric acid in a particular individual. Would you comment on this?

DR. EBSEN KIRK: Yes. The person was an apparently normal young man who had volunteered for a study on the effect of age on the plasma uric acid values. We found that he had a plasma uric acid concentration of between 0.2 and 0.6 mg. per cent, or about one tenth of the normal concentration. In contrast to this, the hypoxanthine-xanthine level of the plasma was fifteen to twenty times higher than normal. We thus had a patient with markedly elevated hypoxanthine-xanthine plasma values and extremely low uric acid values. Incidentally, his relatives were also found to have high hypoxanthine-xanthine plasma values. Since then there have been other reports of hypouricemia in the literature, but I do not think that these cases are quite similar to the one observed by me. Sirota and his associates in 1952 reported the finding of hypouricemia in a patient with Fanconi's syndrome, and Bishop, Zimdahl and Talbot in 1954 observed low serum uric acid values in two patients with hepatolenticular degeneration.

We thought that our patient presented an unusual opportunity for a study of the mechanism of uric acid excretion. For this reason we performed simultaneous measurements of inulin and uric acid clearances. It was found in repeated tests that the uric acid clearance values exceeded the inulin clearance values by approximately 40 per cent and, therefore, we concluded that in this subject uric acid must be partly eliminated by tubular secretion. There is, of course, the other possibility that the higher uric acid clearance, as compared with the inulin clearance, might have been due to a formation of uric acid in the kidney. So far there has been no demonstration of xanthine oxidase activity in renal tissue in man. It is difficult to express an opinion concerning tubular secretion of uric acid under normal or other disease states.

DR. SHERRY: The major area of interest in our patient relates to the nephropathy which led to his premature death. It has been pointed out that renal manifestations in gout are usually so insidious, especially in the early stages, as to be entirely without clincial symptoms and consequently are frequently overlooked. Usually the presence of nephropathy is heralded only by the slight appearance of albumin and a few formed elements in the urine. It is also well recognized that on occasions nephropathy may preceed the first articular bout. Our patient was rejected from military service at the age of twenty because of proteinuria. He had his first articular bout at the age of twenty-four. Dr. Bricker, was the proteinuria an expression of an early gouty nephropathy, or must we give serious consideration to some other underlying chronic renal disease?

DR. BRICKER: The available data do not permit us to make this distinction with certainty. It is possible that the proteinuria was a reflection of asymptomatic hyperuricemia. However, the nephropathy was first noted at age nineteen or twenty. I believe that we must indeed give serious consideration to an independent underlying renal disease such as glomerulonephritis.

DR. SHERRY: I agree. The proteinuria could be either an early manifestation of gouty nephropathy or the presence of some underlying renal disease. Let us consider the nature of renal disease in gout. The pathologic condition of the

kidney in gouty patients who die in renal failure has not been specific. Changes consistent with nephrosclerosis, chronic glomerulonephritis, urate nephritis or pyelonephritis may be interspersed throughout the renal parenchyma and the term "mixed nephritis" has been applied in some instances. How has the pathogenesis of some of these mixed lesions been explained?

DR. BRICKER: When uric acid excretion is increased in gouty patients, as it is not infrequently, the concentration of urate may be greater than normal in the distal tubule and collecting ducts. At a point beyond the region where the urine is acidified, an increased concentration of urate in a pH which promotes crystallization could be responsible for the deposition of intratubular urate debris. This could result in obstruction of individual nephrons which, in turn, favors the development of a number of other abnormalities, including fibrosis of the involved and contiguous nephrons and the development of pyelonephritis. The latter is certainly known to occur with greater frequency in the presence of obstructed nephrons. Finally, calculus formation in the larger collecting radicals would result in obstruction of massive numbers of nephrons, with potentiation of the generalized nephropathy and, in particular, acceleration of the pyelonephritis. There also appears to be an increased incidence of arteriolar nephrosclerosis with relationship to age in a gouty population. However, a cause and effect linkage has not been established to my knowledge.

DR. SHERRY: Some authors restrict the term gouty nephropathy to the deposition of urates in the tubule with an associated tubular obstruction. On the other hand, it is quite apparent that renal disease in gouty patients is due to a number of mixed lesions. The important question is whether nephropathy in gout represents preexisting or independent renal disease which may be aggravated by gout, or whether urate deposits initially damage the kidney and predispose to secondary disease. What does gouty nephropathy mean to you?

DR. BRICKER: I think, Dr. Sherry, the term should be used in a generic sense only to indicate renal failure in the patient with gout. From an etiologic point of view, it has very little meaning.

DR. SHERRY: What lesions do you suspect are present in our patient's kidneys?

DR. BRICKER: First, we must hold to the possibility that there might be an independent lesion unrelated to the gouty diathesis such as, for example, chronic glomerulonephritis. Second, at some point in this patient's course, urate deposits may well have developed in the collecting ducts, although there is no evidence for the deposition of urate in the pelves or ureters. Pyelonephritis seems like a very likely possibility in this patient, and nephrosclerosis also seems likely, even though he was young. Finally, I would suggest that the accelerated hypertensive syndrome he manifested during his final period of life would be reflected by the presence of acute vascular lesions in the renal arterioles.

DR. SHERRY: There are a few other points we should comment on. As you recall, at the time of discharge after the patient's second admission, therapy was switched from Benemid® to salicylates. The administration of Benemid had proved ineffective, and it was hoped that salicylate therapy might reduce the uric acid pool. Unfortunately, severe bleeding of the upper gastrointestinal tract occurred which may well have been attributed to the administration of salicylates. Dr. Shatz, would you comment on the relation of salicylate therapy to acute gastrointestinal bleeding?

DR. BURTON SHATZ: There is a great deal of evidence to incriminate the administration of salicylates as the cause of hemorrhage in the upper gastrointestinal tract. In the past two years, there was a report of a series of such hemorrhages in patients with duodenal ulcers, 75 per cent of whom gave a history of previous ingestion of salicylates. Also, in groups of patients in whom there is no demonstrable disease of the upper gastrointestinal tract as evidenced by the x-ray and gastroscopic examination, there is about a 50 per cent incidence of ingestion of salicylates immediately prior to the onset of hemorrhage. As a result, many investigators have become interested in the mechanism whereby this could occur, and several have been suggested. One with which we are all familiar, is the local tissue irritation which has been observed through the gastroscope in patients following the ingestion of a tablet of aspirin. Under these conditions, hyperemia and even ulceration of the mucosa in contact with the tablet has been seen. Then, too, we are all familiar with the impairment of prothrombin production which occurs in the prolonged use of large doses of salicylates, producing hypoprothrombinemia and a bleeding tendency. Thirdly, it has been demonstrated that ulceration can be produced in the upper gastrointestinal tract by the parenteral injection

of salicylates. Ivy has shown that there is an increased amount of acid secretion, both in man and in animals, following the administration of parenteral salicylates. And lastly, in the past year, Frick reported that in patients who had massive gastrointestinal hemorrhage following the ingestion of salicylates, but in whom gastrointestinal lesions were not demonstrable, it was possible to demonstrate increased bleeding time and increased capillary fragility. This, he has shown, disappears when the administration of aspirin is stopped and recurs when aspirin is readministered. Although this latter mechanism may not occur frequently, it becomes more significant when one considers the fact that in 1944 Gross and Greenburg, investigating the production of salicylate compounds in this country, noted that in one year we produced ten million pounds of salicylates for public consumption.

DR. SHERRY: Following the severe bleeding episode, a rather peculiar or unusual type of diuretic syndrome developed which persisted for a period of six months. During this period the patient excreted as much as 6 L. of water and 15 gm. or more of sodium chloride daily. Dr. Bricker, what do you attribute this to?

DR. BRICKER: It is unusual and we have seen no other comparable patients either personally or in the literature. One possible explanation is that during his bleeding episode, his blood pressure dropped and thereafter acute tubular necrosis developed. However, the prolonged duration of his diuretic syndrome was strikingly different from that noted in the recovery phase of acute tubular necrosis and, I believe, rules out this diagnosis. Another possibility is that he had a period of unrecognized urinary tract obstruction and that he then sustained a postobstructive diuresis. The duration of the latter may be as long as it was in this patient, but we have no evidence of obstruction to support this diagnosis. Finally, the entity which we know as salt-losing nephritis must be mentioned. This can be associated with sustained and occasionally massive salt and water diuresis. Again, the data do not fulfill the criteria for this diagnosis and it seems the least likely of the three mentioned. One cannot escape the thought that this may be a previously undescribed form of diuretic syndrome.

DR. SHERRY: Do you anticipate any histological counterpart of this syndrome?

DR. BRICKER: The physiologic characteristics of this syndrome suggest that the tubular reabsorption of sodium chloride was suppressed, and that the patient was having a persisting spontaneous osmotic diuresis far greater than could be explained by the degree of elevation of urea. Whether or not any histologic lesion will appear on light microscopy is problematic. I seriously doubt it.

DR. SHERRY: On the last admission, the patient was noted to have severe chest pain, which worsened on respiration. A loud pericardial friction rub was readily audible. Although Friedberg states that uremic pericarditis is asymptomatic, Wacker and Merrill noted that 36 per cent of their patients with uremic pericarditis had pain. In all cases it was substernal, and in almost all, pleuritic in character. In almost half the cases, the pain was described as severe and crushing. In the light of these observations I would attribute our patient's chest pain to the pericarditis. The etiology of uremic pericarditis is still obscure: it is most often sterile but, on occasions, may be infected. The average duration of life after the onset of pericarditis in chronic renal failure is ten days. However, on occasion, it may last much longer and even disappear.

As a final clinical diagnosis, I would offer primary gout and uremia secondary to a mixed nephritis. The kidneys should show urate deposits, severe nephrosclerosis and possibly arteriolar necrosis. There is a strong likelihood of an associated pyelonephritis, and a good possibility of an underlying chronic diffuse glomerulonephritis. In addition, we should include a salt losing nephropathy, uremic pericarditis, and hypertensive cardiovascular disease with congestive heart failure. Dr. Harkin will present the pathology report.

PATHOLOGIC DISCUSSION

DR. JAMES HARKIN: The morphologic lesions of the syndrome of chronic gout are similar when produced by several different causes, for example: (1) in primary gout when there is an increased uric acid production associated with an altered metabolic pathway, (2) in secondary gout, most commonly related to an increased breakdown of nuclear nucleoproteins, or (3) in the experimental model, avian gout. Whereas these structural alterations of chronic gout are relatively well documented, the variation in the process that is responsible for precipitation of an acute gouty attack still remains an enigma.

In the case under discussion some of the lesions of gout were illustrated, but only to a slight

FIG. 1. Synovia of the knee. The tissue had been fixed in alcohol. The uric acid crystals can be seen surrounded by hyperplastic synovia. Hematoxylin and eosin, magnification × 300.

FIG. 2. A typical renal glomerulus, illustrating proliferation of the epithelial cells with adhesions. Masson trichrome stain, magnification × 300.

degree. Of the joints that were examined the synovia adjacent to the patella had small inclusions of uric acid crystals. These crystals were surrounded by prominent synovial cells and connective tissue cells. (Fig. 1.) This case had not progressed to that stage in which deposits occur within the adjacent connective tissue and cartilage of the articular surface. No large gouty tophus was available to examine histologically, although one was present in the ear. These tophi are quite dramatic histologically, presenting a central feathered pattern surrounded by a mass of multinucleated giant cells. When such a characteristic pattern is present the diagnosis is not difficult. However it is important to note that in the usual formalin fixation of tissues uric acid is dissolved and the ghosts of the crystals and amorphous masses may pass unnoticed. In this case tissue was fixed in absolute alcohol to retain the uric acid, and it was illustrated prominently by the use of silver stains.

The kidneys were each reduced to approximately half the normal size. Both on gross and microscopic examination only a few crystals of uric acid could be identified in the tubules within the medulla. In cases in which there are massive deposits of uric acid in the renal tubules, these are frequently extruded and surrounded by a foreign body reaction. In these zones it is believed that some of the uric acid may disappear, however the zone then commonly undergoes dystrophic calcification. This process was not present in this case. The other tissues which appear to be altered in gout are the blood vessels, although this may well be some indirectly related pathologic processes which merely parallels the gouty tendency. In the present case, except for those in the kidneys, the arteries and arterioles showed relatively little alteration. In the 550 gm. heart there was a microscopic organizing infarct.

We believed that evidence of alteration of the kidney following uric acid deposition was insufficient to explain renal failure in the present

case. In addition, the kidneys were the seat of alterations bearing all the anatomic stigmas which we associate with chronic glomerulonephritis. Some glomeruli were hyalinized, others were relatively uniformly altered by thickening of basement membranes and proliferation of epithelial and endothelial cells. (Fig. 2.) Glomerular afferent arterioles were severely hyalinized, however, even in the kidneys really classic examples of arteriolar necrosis were not identified. The renal parenchyma contained numerous scars as well as distended and distorted tubules, many filled with casts.

Other features of this case were organizing fibrinous pericarditis, slight secondary parathyroid hyerplasia, severe congestion of stomach and colon, and focal necrotizing stomatitis.

In conclusion this patient presented the morphologic lesions of gout. They were not particularly extensive. He also showed a severe chronic renal impairment which we believe cannot be satisfactorily explained entirely on the basis of uric acid deposits or alteration in uric acid metabolism. At least for the present time, I think it might be useful to limit the term "gouty nephropathy" to those cases in which there are uric acid deposits in the tubules blocking them locally and associated with some form of pyelonephritis or cases in which there is blocking of the collecting duct system with hydronephrosis and pyelonephritis. It seems difficult to extend the concept of gouty nephropathy to include cases which appear to be glomerulonephritis as distinctly as the case today. Would you concur Dr. Sherry?

DR. SHERRY: Dr. Moore, I know that you have discussed the problem of gouty nephropathy with Dr. Talbott. Would you comment?

DR. CARL V. MOORE: The nephropathy of gout is difficult to define. In many instances there is little correlation between the severity of articular gout and the clinical evidence of renal impairment. Urate crystals tend to block the tubules and thus cause atrophy of nephrons; urate deposits, often surrounded by lymphocytes, may be found in the interstitial tissue. Such kidneys are susceptible to infection and to pyelonephritis. There seems to be an increased incidence of vascular changes in the kidneys as well as in other vessels of the body. Some of the microscopic abnormalities resemble those of chronic glomerulonephritis, but not all authorities agree that the pathogenesis of the lesions is identical. It is difficult, therefore, to know how much of the renal impairment is due to the gouty process *per se*, and how much results from other superimposed renal lesions to which the gouty kidney may be particularly susceptible.

DR. SHERRY: It is apparent that if we had excluded the fact that the patient had gout, the course would have been entirely consistent with chronic glomerulonephritis.

Case Reports

Cerebral Mucormycosis*

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In recent years there has been an increasing interest in mucormycosis and a number of new cases have been reported. This infection is caused by fungi belonging to the class Phycomycetes, order Mucorales, and family Mucoraceae [*1*], organisms long considered contaminants and harmless saprophytes. Only sixteen documented cases involving the central nervous system have been reported since 1885, most of these since 1950. A new case of mucormycosis with involvement of the central nervous system is herewith reported, together with a correlative review of all cases found in a review of the medical literature.

CASE REPORT

A pregnant, emaciated twenty-four year old Negro woman, with a history of diabetes mellitus controlled by diet, was admitted to the D. C. General Hospital, in dehydration, shock and coma. The blood pressure was unobtainable, pulse 140; respiration, 30; and temperature, 97°F. The hematocrit was 43 per cent, the leukocyte count was 32,000/cu. mm. with 93 per cent neutrophils. The urine showed 4-plus sugar and 2-plus acetone, but was free of albumin. Blood chemical studies revealed a glucose of 600 mg./100 ml., urea nitrogen of 170 mg./100 ml. and CO_2 combining power of 5.0 mEq./L. (11 volumes per cent). The patient responded temporarily to the administration of insulin and intravenous saline solution but within twenty-four hours again went into shock, which once more responded to the administration of intravenous fluids. Following delivery of a full term, stillborn infant thirty-six hours after admission, she became moribund, going into shock for the third time. This time it was possible to maintain the blood pressure at a low normal level only with continuous intravenous infusion of levarterenol. Some improvement occurred after potassium was administered. The patient was also given digitalis. She continued to be acidotic and hypernatremic; the blood urea nitrogen gradually rose, reaching 400 mg./100 ml., despite copious diuresis. The blood sugar reached 1,440 mg./100 ml. despite therapy. A rachiacentesis revealed blood-tinged fluid containing a few gram-positive cocci. Three days after admission the patient was started on a regimen of cortisone, antibiotics and vitamin K_1 oxide. She became dyspneic, rales, gastrointestinal hemorrhages and multiple areas of purpura developed, including a hematoma of the left periorbital tissues. The platelet count dropped precipitously to 14,000 per cu. mm. The patient was given a transfusion of 1 L. of blood during the hospital course. The state of shock became irreversible, and the patient died five and a half days after admission.

At autopsy the significant abnormal gross pathological findings were confined to the brain, lungs, left orbit, genital tract and kidneys. The brain showed subarachnoid hemorrhage on the left, involving the orbital surface of the frontal lobe, temporal tip and olfactory tract. The inferior frontal subarachnoid hemorrhage extended approximately 1 cm. into the brain substance. The grossly dissectable arteries at the base of the brain and the venous sinuses of the cranium displayed no pathologic condition on gross examination. The lungs were edematous and congested, with multiple foci of hemorrhage. The posterosuperior portion of the lower right lobe was the site of a poorly demarcated, acrepitant lesion of pyramidal shape. The pleural surface was dark red and covered by fibrin. The cut surface consisted of reddish black, consolidated, friable, granular tissue. The branch of the pulmonary artery supplying this portion of the lower right lobe was occluded by a thrombus attached to the intima and consisting of friable, solid, grayish tan tissue. This thrombus extended into the smallest grossly dissectable branches of the vessel. There was massive hemorrhage into the left orbit, the periorbital tissue showing purplish discoloration of the skin and swelling of the subcutaneous tissue. The enlarged uterus measured 24 by 15 by 6 cm., the fundus rising to a level just superior to the umbilicus. The myometrium measured 2 cm. in thickness. The uterus showed diffuse subserosal and myometrial hemorrhage, but its endometrium was thin and intact. The lower uterine segment was thinned, so that a distinct cervical portion was not identifiable. There was massive hemorrhage into the fallopian tubes and left ovary. The kidneys were flabby, with pale cortices showing

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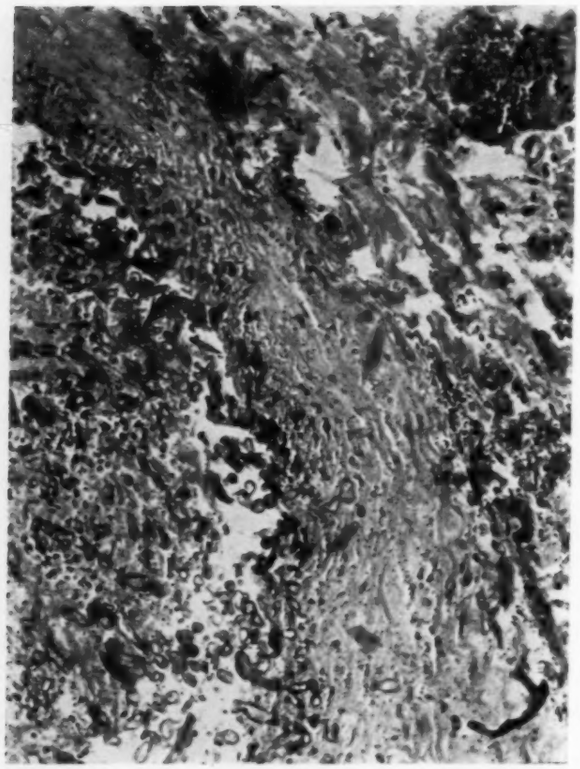

FIG. 1. Mucor in pulmonary vessel with destruction of vessel wall and thrombosis. Hematoxylin and eosin × 100.

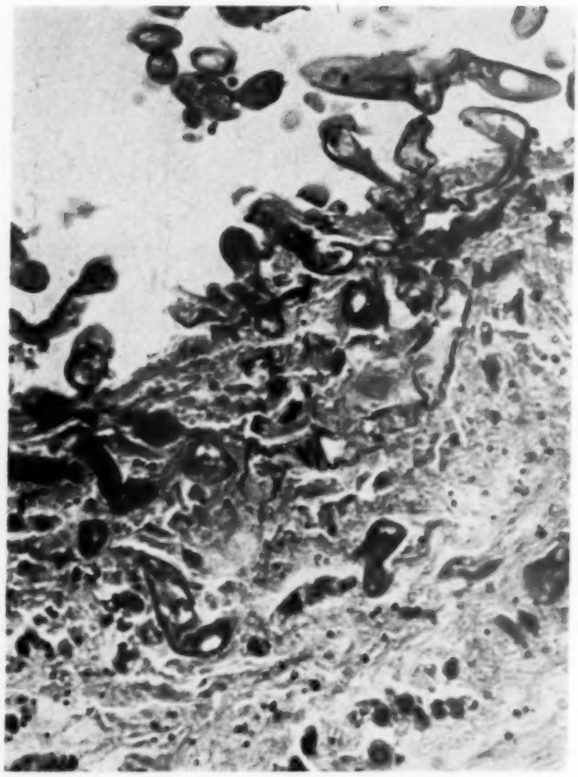

FIG. 2. Mucor invading the meninges of the left frontal lobe. Hematoxylin and eosin × 450.

peritubular hemorrhage, congested medullas and submucosal pelvic hemorrhage.

Additional findings included a bloody discharge from the mouth, nose and right ear, areas of purpura on each leg, petechiae of the peritoneum associated with 150 cc. of serosanguinous ascitic fluid, and petechiae of the epicardium, endocardium, stomach and duodenum. The stomach contained a small quantity of coffee-ground-like material. Pitting edema extended from the feet to the knees. The adrenal cortices were depleted of lipid.

The air-containing sinuses of the head were not investigated as at the time of autopsy there was no suspicion of the true diagnosis, and no other reason to suspect a pathologic condition there. Permission was not given for dissection of the eyes.

Microscopic lesions were most prominent in the lungs, brain, hypophysis, liver and kidneys. The lungs showed generalized edema and hemorrhage. In the pyramidal-shaped lesion from the lower right lobe the hemorrhage was associated with amorphous necrosis of the alveolar walls. Pulmonary veins and arteries of various sizes were filled with thrombi, which were tenuously attached to the intimas and were beginning to organize. The thrombi, vessel walls, infarct and contiguous viable pulmonary tissues were invaded by a fungus. (Fig. 1.) This consisted of wide, branching, aseptate mycelia 6 to 10 microns in diameter and spherical spores 12 to 15 microns in diameter. Many portions of the lungs also were infiltrated by polymorphonuclear neutrophilic leukocytes in areas invaded by the fungi, as well as in some areas not involved in this process. Occasional associated bacterial colonies were also seen. Sections through the left frontal lobe of the cerebral cortex revealed invasion of the leptomeninges (Fig. 2), leptomeningeal and intracerebral blood vessels and a thin layer of the subpial brain substances by a fungus identical with that in the lungs. The affected vessels were congested, surrounded by neutrophilic leukocytes, and many were thrombosed. The cerebellar cortex was the site of an infarct of microscopic size characterized by necrosis, hemorrhage, infiltration with microglial macrophages, and astrocytic proliferation. No fungi were seen in it. The pars anterior of the hypophysis also contained an infarct consisting of amorphous necrotic tissue with peripheral karyorrhexis and neutrophilic infiltration. Contiguous to the infarct there was invasion by a fungus morphologically identical with that in the lung and brain. No fungi were demonstrable in any other organ.

The liver showed fatty metamorphosis and severe centrilobular necrosis consistent with the patient's state of shock. The abnormal findings in the kidneys

included diffuse amorphous necrosis of the convoluted tubules characterized by nuclear chromatolysis and hyaline degeneration of the cytoplasm, cortical peritubular hemorrhage, and the presence of leucine crystals within the lumens of the collecting tubules. There was focal hemorrhage into the thyroid parenchyma. The heart showed some fragmentation of the myocardial fibers, in addition to the focal subendocardial and subepicardial petechiae noted on gross examination. There was hyperplasia of the myeloid cells of the bone marrow.

COMMENTS

Identification of Fungus. The fungus present in the lesions could be identified by its rather typical morphology in tissues as a member of the class Phycomycetes, order Mucorales, and family Mucoraceae. The members of this family are characterized in mammalian tissue by a coenocytic (non-septate) thick mycelium up to 50 microns in diameter with spherical to ellipsoidal spores of similar dimensions [*2*]. This mycelium can be differentiated from the septate mycelium of the Ascomycete Aspergillus, which is superficially similar in tissues [*3*]. Also, occasionally, the typical spherical sporangia of the Mucorales can be seen. The reaction to the fungus is also rather typical, with striking necrosis, infiltration of polymorphonuclear neutrophilic leukocytes (and, in the brain, a macrophagic response), and invasion of arteries and veins with ensuing thrombosis. Although this fungus can be identified as to class and order by its morphology in tissues, further identification as to genus and species can be made only by culture. The usual culture medium is Sabauraud's glucose agar, on which the Mucoraceae grow readily at room temperature [*4*].

Ecology of the Mucoraceae. The Mucoraceae are widespread in nature [*5*]. They are sometimes called "sugar fungi" because of their ability to break down carbohydrates. In sugar-enriched substrates they grow rapidly and readily sporulate under aerobic conditions [*6*]. Normally saprophytic [*6*], they are common contaminants [*17*].

Under certain conditions, probably related to their sucrophilia, they can become pathogenic [*8*] for man and animals. Spontaneous infections have been observed in birds [*9,10*], dogs [*11*], pigs [*12,13*], horses [*14–16*] and cows [*17–19*]. The type of lesion, organs affected, and pathogenic genera are similar in animals and man. Mucor corymbifer has been cultured from bovine cases [*20*], and the genera Rhizopus and Absidia from swine [*12,13*]. Lichtheim [*21*] in 1884 was the first to prove the pathogenicity of Mucor corymbifer and Mucor rhizopodiformis for rabbits when he injected the spores of these fungi intravenously, resulting in widespread abscesses and eventually death of the animals. In 1886 Lindt [*22*] similarly demonstrated the pathogenicity for rabbits of Mucor pusillus and Mucor ramosus. The disease is rarely if ever found in otherwise normal human beings. Motta [*23*] took specimens for culture of fungi from the nose and throat of 110 people (thirty-six were normal, seventy-four diseased). He found Mucor species in two of the diseased group.

Infection in man was first described by Cohnheim, who reported a pulmonary infection in 1865, according to Kurrein [*24*]. However, the first well documented case was reported by Paltauf [*25*] in 1885 in Germany. This is also the only reported case of widely disseminated infection involving multiple organ systems. The organs most commonly infected are probably the lungs and ears [*26*]. A few cases have been reported in the gastrointestinal tract [*27–33*], skin [*34–48*] and palate [*39,40*]. Until 1950 there were only six cases involving the central nervous system. As twelve cases, including the one reported here, have been reported since that time, it would appear that the incidence is increasing. Unfortunately, in only a few instances have cultures for fungi been performed. This is chiefly because the disease usually has been unsuspected during life and diagnosed only from the microscopic sections. The genus Mucor was cultured in a case by Watjen [*41*] in 1929, Rhizopus arrhizus [*40*] from a palatal ulcer, and Rhizopus oryzae in three instances—in one case of palatal infection [*39*] and in two of cerebral involvement (in the first the specimen for culture was obtained from the ethmoid sinus [*6*] and in the second from the eye) [*42*].

Review of Literature and Analysis of Cases. Table 1 summarizes the findings in the eighteen cases of cerebral mucomycosis which have been reported. There was an age range from seven days to seventy-five years. Males and females appear to have been equally affected. Twelve of the patients were white, six Negro.

Predisposing conditions: The factors which appear to be related to and probably predispose to infection by Mucoraceae are similar in cases with central nervous system and in those with systemic involvement.

TABLE 1

CEREBRAL MUCORMYCOSIS

Case No.	Year	Author	Age (yr.)	Race	Sex	Orb. Fron.*	Involvement of Orbit		Paranasal Sinuses		Other Organs	Fungus Culture	Diabetes Mellitus	Acidosis of Any Cause	Steroids	Antibiotics	Other Diseases
							Clinical	Microscopic	Clinical	Microscopic							
1	1885	Paltauf	52	W	M						Disseminated		−		−	−	
2	1943	Gregory et al.	43	N	F						Hypophysis, cerebral vessels		+	+			Syphilitic nephritis
3	1943	Gregory et al.	52	N	F		+	OM†		+	Nose		+	+			Hyaline islets of Langerhans
4	1943	Gregory et al.	75	W	M		+	+			Hypophysis		Prob.				Cirrhosis, hyaline islets, glycogen in renal tubules and liver cell nuclei
5	1947	LeCompte and Meissner	57	W	M		+				—		+	+	−	−	Hemochromatosis, generalized
6‡	1949	Wolf and Cowen	42	N	M	+			+		Cavernous sinus		+	Prob.	−	+	Glomerulosclerosis, uremia
7	1950	Stratemeier	32	N	F		+			+	Nasal turbinate		+	+			Acute alcoholism
8	1954	Kurrein	5 mo.	W	M	+					—		−	Prob.	−	+	Acute nephritis, uremia
9	1954	Martin et al.	2½ mo.	W	M	+	+	+			Face, esophagus, lungs, pancreas, marrow, internal carotid artery		−	+	−	+	Dehydration, cachexia
10	1955	Bauer et al.	25	W	F		+				—	Spinal fluid, unidentified yeast	+	+	−	+	Kimmelstein-Wilson's disease, nephrosclerosis, renal papillary necrosis, atherosclerosis
11	1955	Bauer et al.	40	N	M		+	+	+	+	Nose, internal carotid artery	Ethmoid sinus, Rhizopus oryzae	+	+	−	+	Splenic infarct
12	1955	Gunson and Bowden	8	W	F						Internal carotid and middle cerebral arteries		−	Prob.			Chronic glomerular nephritis with uremia
13	1956	Fouskee and Beck	65	W	F		+				Probably nose as in olfactory bulbs		−	−	−	+	Eight days postcholecystectomy, liver abscess, carcinoma kidney
14	1956	From Med. J. Australia	53	W	F			+			Lungs		+	+	−	+	
15	1957	Jackson and Karmauchow	7 days	W	F		+				Ileum (perforation)		−	−	−	+	Pulmonic stenosis
16§	1957	Torack	64	W	M						Heart, lungs, spleen, stomach		−	Prob.	+	+	Multiple myeloma, uremia
17	1957	Merrium and Tedeschi	57	W	M		+	+		+	Hypophysis, int. carotid artery and branches	Sputum and sphenoid sinus, yeast unidentified	+	+	−	+	Coronary atherosclerosis, old myocardial infarct
18	1958	Long and Weiss	24	N	F	+	+				Lungs, hypophysis	Formalin-fixed tissue negative	+	+	+	+	Postpartum, shock, renal tubular necrosis, centrilobular hepatic necrosis

NOTE: Blank spaces = not investigated or information unavailable.
* Orb. Fron. = orbital surface frontal lobe.
† OM = ocular muscles.
‡ = paranasal sinuses infected on x-ray.
§ Case 16 = meninges only, not brain.

Since Mucoraceae are rarely found in normal persons, the pre-existing conditions which are associated with mucormycosis must be considered. They are (1) uncontrolled diabetes mellitus, (2) acidosis due to any cause, (3) antibiotic therapy, (4) therapy with ACTH and the adrenal cortical hormones, and (5) miscellaneous conditions. Of these, diabetes seems to be the most important. It was definitely present in ten cases, and probably in one other. Moreover, this has been the primary pathologic process in the majority of cases of mucormycosis involving multiple organ systems [*4,39,52*]. However, it is not due to hyperglycemia since diabetes *per se* is not enough. There is a great abundance both of the Mucoraceae and of diabetes, but relatively few diabetic patients have mucormycosis. Study reveals that the diabetes must be uncontrolled [*4,39,52*]. In the series of cerebral cases, of ten patients with diabetes, nine were in acidosis and the tenth was possibly in this state. Also, in another patient who possibly had diabetes there was some clinical evidence that the patient was also in acidosis. These facts are confirmed by experiments with animals. In rabbits with acute alloxan diabetes Elder and Baker [*53*], by intratracheal instillation of spores of Rhizopus arrhizus taken from an infected patient, produced severe pulmonary mucormycosis, with necrosis, vascular thrombosis and abundant hyphal growth. Injection into normal control subjects and rabbits with chronic alloxan diabetes produced this disease only when there was a heavy inoculation, and, in general, the spores failed to germinate. Schofield and Baker [*54*] elicited similar results in mice although the routes of injection were intraperitoneal and intracerebral rather than intratracheal, and the organs infected consequently different. How does chronic alloxan diabetes differ from the acute form? In the acute stage of alloxan diabetes there is a high blood sugar, peripheral vascular collapse, lethargy and ketosis, somewhat comparable to diabetes with coma in man. On the other hand, in the chronic stage, which occurs a few days later when the animal has partially accommodated to his disease, a condition resembling the controlled disease in man results, with a more stable hyperglycemia but no ketosis. It would seem, therefore, that ketosis may be an important factor favoring *in vivo* growth of Mucoraceae. *In vitro*, Dubos [*55*] demonstrated that ketone bodies partially protect tubercle bacilli from the bactericidal effects of lactic and acetic acids. Probably, this is likewise true for fungi. The leukocytes appear to be concerned in this problem. Martin and his co-workers [*56*] found that leukocytes from diabetic persons produce less lactic acid than those from normal persons, and Bauer et al. [*57*] observed nuclear degeneration in the polymorphonuclear leukocytes from rabbits with acute alloxan diabetes. The high susceptibility of animals with acute alloxan diabetes to mucormycosis is not due to diminished neutrophilic response [*58*]. It may be partially attributable to the lowered body temperature [*53*] and to the absence of phagocytosis of the spores by macrophages [*53*], but ketosis is probably the most important factor, possibly by affecting the white blood cells in the way described.

Acidosis of any cause, diabetic or otherwise, may favor the development of mucormycosis. In the eighteen cerebral cases, six patients had serious renal disease. Of these six, four were definitely in uremia, and acidotic. Furthermore, of the total of eighteen cases there were ten of definite acidosis and five more of probable acidosis (the laboratory data were unavailable in these five, from which Paltauf's case is excluded as there is no evidence in it of acidosis), this being chiefly the ketotic acidosis of diabetes, but also including the four cases of uremia and one of infantile dehydration in which ketosis may have been a factor. In several of these patients the diabetes was complicated by renal insufficiency, which makes it difficult to ascertain whether the acidosis was due to uremia or diabetic ketosis, but at least three were nondiabetic patients with uremia. It thus appears that acidosis, diabetic or otherwise, may predispose to mucormycosis.

A third factor to be considered is antibiotic therapy [*32,52,59*]; eleven of the eighteen patients received these drugs, two did not, and no information is available for the others. Torack [*50*] reported a series of thirteen cases of fungus infection in patients given antibiotics, the adrenal cortical hormones and ACTH. All had other primary diseases, chiefly hematopoietic, but none were diabetic. The fungi present were Monilia, ten cases; Aspergillus, three cases; and Mucor, three cases. All the more common antibiotics except Aureomycin® were incriminated in this report. Several possible mechanisms of action have been postulated. (1) Stimulation of growth: Aureomycin, bacitracin and neomycin stimulate the proliferation of Monilia *in*

vitro [*60,61*]. De Mello [*62*] noted potentiation of fungal growth by derivatives of aureomycin with no antimicrobial activity. (2) Enhancement of virulence: An increase in virulence of fungi in mice given Aureomycin and Terramycin® has been claimed by Seligman [*63,64*]. However, both these mechanisms are denied by others [*62,65,66*]. (3) Depression of antibody titer: this has been demonstrated in animals after prolonged feeding of antibiotics [*67,68*]. (4) Alteration of the bacterial flora permits fungi to proliferate [*69–71*]. (5) Toxicity to tissues may be a factor, as is known to be true of Aureomycin [*72*]. It is possible that all these modes of action may be pertinent in patients treated with antibiotics.

A fourth factor which probably plays a part in the predisposition to mucormycosis is therapy with ACTH and the steroid adrenal cortical hormones. As only two of the patients listed in Table 1 were thus treated, it is obviously impossible to draw any conclusions from them. However, the findings of Torack [*50*] cannot be disregarded. This investigator, as previously mentioned, reported thirteen cases of fungus infection all of which were treated with antibiotics and these hormones. The hormones implicated were ACTH, cortisone, corticotropin, prednisone and hydrocortisone. Their importance has also been noted by others [*4,32,52*]. Baker et al. [*73*] found that rats, mice and guinea pigs treated with cortisone were more susceptible to experimental peritoneal infection with Rhizopus oryzae than were control subjects, and that, moreover, the infection showed a greater tendency to spread. Antopol [*74*] has reviewed the effects of cortisone therapy and points out a great increase in susceptibility to a wide variety of infectious agents. However, Bauer and his co-workers [*75*] found that the administration of cortisone did not decrease the resistance of rabbits to artificially produced mucormycosis (with Rhizopus oryzae spores) as much as did acute alloxan diabetes.

The following modes of action have been suggested: (1) decreased adherence of leukocytes to the vascular endothelium [*76–78*], (2) diminished phagocytosis [*79,80*], (3) decreased blood flow due to increased arteriolar tone [*50*], (4) diminished liberation of leukotaxine by injured cells, resulting in depression of the leukocytic response [*81,82*], (5) depression of fibroblastic proliferation, (6) inhibition of antibody response, and (7) blocking of the antigen-antibody reaction. The finding of a decrease in the total lymphoid mass in such cases points to a depression in synthesis of antibody [*83–86*].

In summary, the chief factors predisposing to mucormycosis appear to be ketosis, other acidoses, treatment with antibiotics, and use of corticosteroid hormones and ACTH.

Sporadic cases of mucormycosis have also been associated with leukemia [*4,52,59,87,88*], therapy with antileukemic drugs [*4,52*], burns [*4,52,87*], syphilis [*26*], Laennec's cirrhosis [*26*], hemochromatosis [*43*], acute alcoholism [*45*] (this patient also had diabetes), pulmonic stenosis [*49*], multiple myeloma [*50*], kwashiorkor [*33*], and cholecystectomy [*47*]. Finally, in our case, the patient was postpartum, in addition to being in diabetic coma.

Pathogenesis: The ubiquitous Mucoraceae have been frequently observed as contaminants of the skin and natural body orifices [*7*], occasionally giving rise to a dermatitis [*35–38*] as previously noted, to cases of paronychia in orange pickers [*34*] and sometimes to external otomycosis [*34*]. By inhalation and ingestion the spores may also find their way into the nose and mouth. From these sites invasion of the body can occur by three routes: (1) the vascular system, (2) the natural passages, and (3) local tissue spread. The first pathway has been noted by all observers, as these fungi have a marked predilection for blood vessels, both veins and arteries, growing through the walls into the lumens, with ensuing thrombosis. This produces local infarction. It is believed that these fungi cause tissue damage chiefly by interrupting the blood supply. The second mode of spread, via the natural passages, results in gastrointestinal and pulmonary pathology from the oro- and nasopharynx. In a case of kwashiorkor associated with gastric mucormycosis recently reported in a child from South Africa by Watson [*33*], the inability to find the fungus in any other organ led to the conclusion that the infection could only have resulted from ingestion of the spores with subsequent spread via the esophagus. The third mode of spread, local tissue invasion, no doubt occurs in all forms of the disease, but is especially conspicuous in the cerebral type.

Cerebral mucormycosis can apparently arise in two ways: (1) by embolism by way of the blood stream from a primary source anywhere in the body or head, and (2) from a primary source in the head, by local tissue extension. Of all primary foci, it seems that the most common source

is the head itself. This source is difficult to evaluate because the orbit, nose, mouth, ears and bony portions of the head are rarely examined at autopsy. However, study of the clinical evidence of disease in these areas and the findings in the few cases which have been explored leads to certain conclusions. Of the eighteen cerebral cases, there was only one case (Case 12) in which the only organ system apparently involved was the central nervous system. There were only three cerebral cases associated with mucormycosis widely disseminated throughout the body; in one of these (Case 16) the only intracranial involvement was the meninges. Of the series of eighteen cases, there was infection outside the head in only six, or one-third of the total. Conversely, in two-thirds, or in twelve cases, the head alone was invaded by the Mucoraceae. In only three cases was there evidence to suggest that of the tissues of the head only the brain was infected. Extracerebral parts of the head were either definitely or probably involved in fifteen cases, or in five-sixths of the total. Microscopic proof of such extracerebral cranial disease was obtained in nine cases.

Within the extracerebral portion of the cranium, the Mucoraceae seem to have a predilection for two sites: (1) the eye, and (2) the paranasal air sinuses. Indeed, orbital infestation has been very striking. Clinical evidence of orbital cellulitis with edema and hemorrhage was present in twelve cases. This was confirmed (by microscopic examination) in six, and in one other (Case 3) the fungus had invaded the extraocular muscles but not the eye itself. One patient showed both clinical and pathological evidence of orbital mucormycosis, coupled with invasion of the orbital surface of the frontal lobe of the brain. These pathologic data, together with the fact that in three other cases there was infection of this portion of the cerebrum although without microscopic demonstration of the fungus, and the fact of the proximity of the two areas, leads to the conclusion that invasion of the orbital surface of the frontal lobe is good if not definite evidence of orbital mycosis. Considering both clinical and pathological evidence, in fourteen of the eighteen cases there was either definite or probable orbital mucormycosis. Because of the high percentage of orbital involvement (78 per cent), the proximity of the eye to the brain, and the conspicuous infiltration of portions of the brain nearest the orbit, the eye probably serves as a source of infection of the brain in mucormycosis.

The evidence for infection of a high percentage of the paranasal air sinuses is not as conclusive as that of the orbit. This may well be due to the external position of the orbits, which renders disease there more easily recognizable than in the sinuses. There is evidence that the sinuses were investigated microscopically in only four instances, in each of which the fungi were found. However, a consideration of the clinical data leads to the conclusion that in six cases the sinuses were either definitely or probably involved. It may be concluded that the sinuses may also be a significant source of infection for the brain in mucormycosis. In seven cases there was evidence of lesions in both the orbit and another portion of the face (sinuses, nose, etc.).

In this series of eighteen cases, of the four patients with microscopic proof of sinus infection, fungi were seen in the nose of three. In another in which there is no statement as to whether the nose or sinuses were explored, (Case 13) the olfactory bulbs were heavily infested. It thus appears highly probable that the nose is a primary portal of entry, also. A study of the five cases of cranial mucomycosis in which the patients survived yields further interesting data. At least two showed evidence of cerebral disease. There was proof of infection of the palate in two cases, the eye in two cases, the sinuses in two, and the nasal septum in one. In one case the fungi were found in both the eye and the nasal septum, and in another in three sites, eye, palate and sinuses.

From these data it is possible to draw certain conclusions regarding the pathogenesis of the majority of cases of cerebral mucormycosis. The portals of entry appear to be the nose, mouth, and possibly also the eye by direct infection. The fungi may even exist as saprophytes in the nasopharynx and oropharynx, invading under propitious conditions. The infection may spread either by local infiltration of the tissues or by the blood and lymphatic channels. From the mouth the fungi invade the palate, and from there the paranasal air sinuses. From the nose, infection proceeds (1) into the sinuses, (2) through the cribriform plate into the meninges and brain, and (3) through the nasolacrimal canal into the orbit. The brain may be secondarily involved (1) from the sinuses, (2) from the orbit, (3) through the cribriform plate, and (4) from extracranial foci by hematogenous dissemination.

Prognosis: Until 1955 systemic mucormycosis was always a fatal disease but the outlook is now somewhat more favorable. Since 1955, six cases have been reported in which the patient recovered [*4,39,40,42,89*]. Of these, one was pulmonary and five were cranial. Of the five cases involving the head, there was clinical evidence in two that the central nervous system was involved. These cases are not included in Table 1, as in neither case was the clinical diagnosis confirmed by culture or microscopic identification of the fungus in either the brain or cerebrospinal fluid. The clinical diagnosis was confirmed in all but one case by biopsy, culture or both. All six patients were uncontrolled diabetics. In addition to the control of the diabetes in all instances, other forms of therapy used in one or more cases were: potassium iodide, desensitization to the fungus, parenzyme and Mycostatin.® In only one case, that of Georgiade and his co-workers [*39*], are antibiotics listed as part of the treatment, while McCall and Strobos [*42*] stress the fact that administration of these drugs was stopped in their patient. It would seem that the use of these drugs is contraindicated from the data already presented. In two cases surgical excision of the focus of infection was necessary.

Analysis of Case of Cerebral Mucormycosis Herein Presented: The case of mucormycosis presented in this paper (Case 18) is that of a twenty-four year old pregnant Negro woman. She was admitted to the hospital in diabetic coma and shock, was delivered of a full-term stillborn infant thirty-six hours later, and died five days after admission. At autopsy, evidence of shock was found. This was the result of two conditions: (1) diabetic coma, and (2) mucormycosis. The diagnosis of diabetes mellitus could be made only from the clinical data, as there were no anatomical stigmas of this disease.

Comparison of this case with the other seventeen in Table 1 reveals many similarities. The fungus was found in the lungs, left frontal and left temporal lobes of the cerebral cortex, and in the cerebellum and hypophysis. Although unfortunately the orbit was not examined microscopically, consideration of its gross appearance and the fact that there was either probable or definite orbital mycosis in thirteen of the other seventeen cases of proved cerebral mucormycosis makes it almost certain that it was also infected in this case. The predisposing factors here are the major ones observed in other cases of this disease, i.e., diabetes mellitus with acidosis, the use of corticosteroid hormones, and the antibiotic therapy. Stress associated with parturition was no doubt another factor. Because of the marked leukocytosis on admission, it is highly likely that the patient had her mycosis at this time, as there was no evidence of any other inflammatory or necrotic process to explain this feature, even though there was no indication of an orbital abnormality until five days later. Possible portals of entry were the vascular system from parenteral injections, and the nose and mouth. If the disease was present on admission, the parenteral route from medication and fluids given in the hospital can be ruled out. One can also eliminate this route prior to the hospital stay, as the patient had not been taking insulin, nor was there evidence that she had been receiving injections of any other drug. This leaves the nose or mouth, the orifices which appear to be incriminated as the portals of entry in the majority of the preceding seventeen cases. It seems probable that from here the fungi spread in typical fashion directly through the tissues and by the blood vessels to the brain by two pathways: (1) through the cribriform plate, attacking the hypophysis and cerebellum, and (2) via the nasolacrimal canal into the left orbit, and from there to contiguous portions of the left frontal and temporal lobes. It is not known whether or not the paranasal sinuses were infected, as they were not investigated at autopsy. From the nose and throat, infection also spread via the trachea and bronchi to the lungs. In all the infected areas the fungus grew through the walls of both arteries and veins, producing thrombosis, with consequent infarction of the tissues affected. The striking neutrophilic infiltration of these infarcted foci can be correlated with the clinical leukocytosis. The possibility that the cerebral infection arose by embolization from the lungs instead of directly from the nasopharynx is unlikely because the intracerebral arteries were free of thrombi and emboli, and there was no evidence of lesions in the chest until the day before death.

SUMMARY

A case of cerebral mucormycosis, the eighteenth proved case in the medical literature, is reported.

The conditions most commonly predisposing to mucormycosis appear to be uncontrolled diabetes mellitus, acidosis of any cause, and the

use of corticosteroid hormones and antibiotics. Cerebral mucormycosis is found in persons of all ages, and is distributed equally between the sexes. The most typical clinical findings are unilateral panophthalmitis (usually with periorbital hemorrhage) associated with diabetic coma and accompanied by neurological abnormalities. Diagnosis can be established by demonstration of the fungus in the cerebrospinal fluid, or in tissues accompanied by an inflammatory reaction. Definitive diagnosis as to genus and species can only be made by culture. The usual portals of entry are the nose and mouth, the infection proceeding by direct invasion to the brain, or indirectly by first invading the palate, paranasal air sinuses and orbit. Dissemination occurs by the vascular system, producing phlebitis, arteritis and thrombosis, with ensuing infarction of the affected tissues, and by direct infiltration of tissue.

Although cerebral mucormycosis is nearly always fatal, two cases with clinical evidence of cerebral involvement have been reported in which the patients recovered.

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A Clinical and Metabolic Study of Metastatic Carcinoid*

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THE relationship between disordered tryptophan metabolism and the syndrome of malignant carcinoid has recently been well established [*1–3*]. The development of a simple quantitative determination of total urinary 5-hydroxyindoles (5-HI), of which 5-hydroxyindoleacetic acid (5-HIAA) constitutes approximately 75 to 80 per cent, has greatly facilitated both the diagnosis and clinical study of this syndrome [*4*]. It is the purpose of this paper to present a long term clinical and metabolic study of a patient with metastatic carcinoid tumor whose urinary excretion of 5-HI has been followed under the influence of various physiological and pharmacological agents.

CASE REPORT

The patient was a fifty year old woman who in 1948 had onset of pain, tenderness and throbbing in the right parietal region. She was seen at another hospital where a diagnosis of right occipital neuralgia was made, but occipital neurectomy afforded no relief. It was subsequently concluded that the patient was suffering from involutional melancholia and she was treated with electric shock and bilateral frontal topectomy.

For the next seven years the patient's symptomatology was mild, but in the early part of 1956 she again experienced severe right occipital throbbing headaches which were not relieved by medication. In addition, she noticed the onset of occasional wheezing episodes, particularly in the morning, and had several bouts of frequent loose bowel movements. Her sister noticed that the patient's lips appeared bluer than previously.

In July 1956 the patient was admitted to the Division of Neurology of the Montefiore Hospital. Physical examination revealed a well developed, well nourished white woman complaining of severe right-sided headache but appearing neither acutely nor chronically ill. The blood pressure was 130/80 mm. Hg, pulse 84 and regular, respirations 18 per minute and temperature 99.4°F. There was slight cyanosis of the lips but no telangiectasia or cyanosis elsewhere. Bilateral frontal topectomy scars were present and there was tenderness over the right posterior occipital region. The thyroid was not palpable and the heart and lungs were clear to percussion and auscultation. The liver was palpable one fingerbreadth below the right costal margin but no other masses were palpable. Rectovaginal examination was negative for abnormalities. The only positive neurological finding was a Hoffman reflex on the right.

On admission, the urinalysis was normal. The hematocrit was 39 per cent; white cell count 5,000 per cu. mm. with a normal differential count; blood platelets 360,000 per cu. mm. The blood urea nitrogen was 13.3 mg. per cent; the serum electrolytes were normal; calcium 8.5 mg. per cent; phosphorus 4.3 mg. per cent and alkaline phosphatase 7.6 Bodansky units. The total protein was 7.7 gm. per cent with albumin 4.2 gm. per cent and globulin 3.5 gm. per cent. Serum electrophoresis showed a normal pattern except for a slight increase in gamma globulin. The prothrombin time was fourteen seconds with a control of twelve seconds; the cephalin flocculation test was negative; thymol turbidity test 5 units; total serum bilirubin 0.39 mg. per cent; Bromsulphalein® test showed 10 per cent in the serum after forty-five minutes; the serum transaminase was 25 units. An electrocardiogram showed regular sinus rhythm with no abnormalities. An electroencephalogram showed delta activity on the entire left side of the head with a suggestive predominance over the left temporal lobe. Chest x-ray film was normal and roentgenograms of the skull were negative except for surgical clips in the frontal and occipital areas. A basal metabolic rate was +9; a radioactive iodine uptake test was 22 per cent after twenty-four hours. Lumbar puncture showed normal dynamics, no cells, and a protein concentration of 21 mg. per cent. The blood Wassermann reaction was negative.

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Two weeks after admission the patient had an acute attack of pain in the right upper quadrant with radiation to the right subcostal and scapular region. A temperature of 104°F. developed with spasm and tenderness of the right upper quadrant, and a leukocytosis of 18,000 with a shift to the left. A diagnosis of acute cholecystitis was made, and laparotomy performed. At operation, however, the gallbladder was found to be normal but the liver was massively infiltrated with yellow-gray nodules. One of these nodules located in the right lobe of the liver appeared necrotic and was biopsied. The body of the pancreas felt hard and nodular but no biopsy specimen was taken. Palpation of the large intestine and appendix was negative but the small bowel was not explored. Microscopic examination of the liver nodule revealed the presence of an epithelial neoplasm which resembled carcinoid tumor such as is seen in the appendix, gastrointestinal tract and elsewhere. In view of these findings, the urine was examined for total 5-hydroxyindoles (5-HI) and it was found that the patient was excreting 105 mg. per twenty-four hours.

In the year since the discovery of the metastatic tumor the patient has done very well. Her weight has remained stable, her appetite is good and she is semiambulatory. The liver has increased in size and is grossly nodular to palpation. The heart and lungs remain clear to percussion and auscultation. Her face has begun to show a definite flushed appearance and she has intermittent periods of frequent, loose bowel movements. X-ray films of the upper and lower gastrointestinal tract and of the sinuses, as well as sigmoidoscopy have failed to reveal the primary site of the tumor.

Comment: Several aspects of this case are noteworthy. The first is the accidental discovery of metastatic carcinoid tumor at the time of surgery for what was presumed to be acute cholecystitis. That this tumor may lead to a mistaken diagnosis of gastrointestinal or cardiovascular disease is not unusual and has been previously reported [*2*].

The most severe and relentless aspect of this patient's course has been her headaches. These have defied attempts at therapy. It is interesting to speculate that the onset of the patient's headaches in 1948 might be related to the carcinoid tumor. We know of no similar occurrence of this symptom as a manifestation of the metastatic carcinoid syndrome and believe that they may be unrelated. Clinical manifestations of "hyperserotoninemia" have been minimal and are confined to intermittent wheezing, flushing of the face, occasional bouts of severe diarrhea and mild cyanosis of the lips. The patient's urine has shown a consistently high excretion of 5-HI. Recent reports seem to establish this finding as pathognomonic of metastatic carcinoid tumor. In 1,120 urine specimens taken from 1,023 patients at the Massachusetts General Hospital no false positive reactions were found [*5*]. In a study from the National Institutes of Health, seventy-two patients with various diseases other than carcinoid tumor were studied and none had urinary 5-HIAA excretions greater than 12 mg. in twenty-four hours [*6*].

METABOLIC STUDY

The patient was under study for a period of 336 days, during which time daily determinations of urinary 5-HI excretion were carried out. Unless otherwise specified, the patient was maintained on a regular hospital diet containing 80 gm. protein, 200 gm. carbohydrate and 95 gm. fat. The average tryptophan content of the diet was 750 mg. daily. The patient was ambulatory throughout. In addition to daily determination of 5-HI excretion, twenty-four hour urinary creatinine values were measured.

The quantitative dertermination of 5-HI was made according to a modification [*7*] of the original method described by Udenfriend et al. [*4*]. The test is based on the development of a purple color specific for 5-hydroxyindoles on the addition of 1-nitroso-2-naphthol and nitrous acid. After the addition of ethylene dichloride, the separated aqueous color phase was read in a spectrophotometer at 540 mμ and compared to a standard curve.

Results. The effect of various oral and parenteral agents on the urinary excretion of total 5-HI is shown in Figure 1. It should be noted that during the 336 days of the study the average excretion rose from 94 mg. per twenty-four hours at the beginning to 166 mg. per twenty-four hours at the end of the study. This we believe reflects progressive growth of functioning tumor tissue. The daily variation in excretion of 5-HI during the period of study we believe to be due at least in part to variation in tumor activity.

Histamine: On separate days, 2.5 mg., 3.0 mg. and 5 mg. of histamine diphospha e diluted in 500 cc. of 5 per cent glucose in water were given by intravenous infusion over a two-hour period. The patient demonstrated the typical manifestations of a histamine reaction with mild wheezing, slight fall in blood pressure and facial flushing. There was no significant change in the excretion

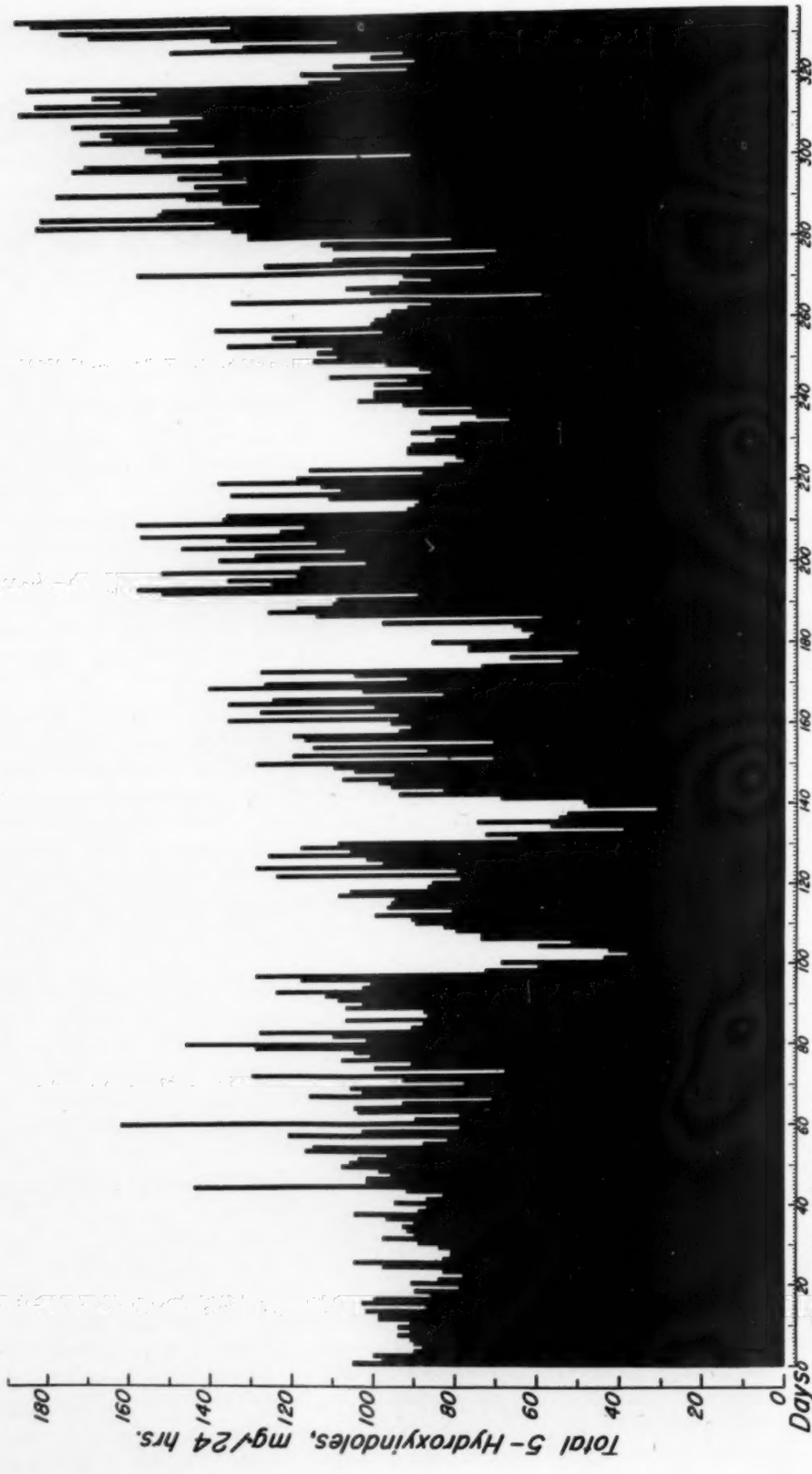

FIG. 1. Effects of various metabolic agents on urinary excretion of total 5-hydroxyindoles in a patient with metastatic carcinoid.

of 5-HI during the days when histamine was administered.

BAS: The benzyl analog of serotonin (BAS)* was given to the patient in oral doses of 200 to 300 mg. per day for nine days. There was no significant change in the patient's excretion of 5-HI nor any fall in blood pressure. Not only was there no amelioration of symptoms but the patient's nausea, vomiting and diarrhea appeared to increase during the period of BAS administration

Tryptophan: Oral tryptophan loading, using DL-tryptophan, giving 500 mg. the first day, 1,000 mg. the second day and 1,500 mg. the next three days, did not significantly increase the excretion of 5-HI, nor did a single intravenous dose of 2.2 gm. of L-tryptophan. At a later date giving 1,500 mg. of L-tryptophan a day orally for three days resulted in a 40 per cent increase in urinary 5-HI excretion on the third day. Still later in the study, 5.0 gm. of L-tryptophan given orally increased the urinary excretion of 5-HI from an average of 145 mg. per twenty-four hours to an average of 168 mg. per twenty-four hours on the day of the dose and the two following days.

Chelating Agents: Beta-N-hydroxyethylethylene diaminetetraacetic acid (versonel), calcium cyclohexanediamine trans 1,2-diaminetetraacetic acid (Ca CDTA), calcium di-sodium ethylenediaminetetraacetic acid (Ca EDTA), disodium ethylenediaminetetraacetic acid (Na EDTA), each given intravenously over a period of four hours, on separate days at a dosage of 2 to 4 gm. diluted in 500 cc. of 5 per cent glucose in water, failed to influence significantly the excretion of 5-HI.

Reserpine: The oral administration of 1 to 2 mg. of reserpine was associated with a rise in excretion of 5-HI to 162 mg. in twenty-four hours, on the first day. However, despite continued administration of reserpine for the next eleven days, subsequent excretions were not markedly elevated. The administration of reserpine was associated with increased severity of the patient's diarrhea. At two subsequent times in the study the patient was given reserpine intramuscularly and orally with no effect on urinary excretion of 5-HI.

Chlorpromazine: A striking effect was obtained from chlorpromazine (Thorazine®) given orally at a dosage of 100 mg. per day. This resulted in a progressive fall in the values of 5-HI to a low of 39 mg. per twenty-four hours with a progressive return to previous levels when administration of the drug was stopped. The same procedure repeated later, using 100 mg. intramuscularly daily, gave similar results. As will be explained, this decreased excretion is only apparent, due to interference by the drug with the analytical method. When the specimens of urine collected during the period of chlorpromazine administration were analyzed by the chromatographic method of Curzon [8], it was found that the results were approximately twice as high as those obtained by the chemical method used in this study. (Table 1.) During a period when the patient was receiving no drug, there was no significant difference between the amounts recovered in the urine by the chemical and chromatographic methods. During the period of chlorpromazine administration the patient's diarrhea subsided, the bowel movements decreasing from two to three to zero to one per day and the stools becoming of normal consistency.

TABLE 1
URINARY EXCRETION OF 5-HI IN PATIENT WHILE RECEIVING CHLORPROMAZINE

Day	Chemical Method		Chromatographic Method	
	mg./100 ml.	mg./24 hr.	mg./100 ml.	mg./24 hr.
135	5.4	57	9.7	102
137	5.0	55	8.6	95
138	4.9	53	9.5	134
139	2.5	31	8.7	109

Methimazole (Tapazole®) and Lugol's solution: Following baseline evaluation of thyroid function which gave the following results: basal metabolic rate +9; radioactive iodine uptake, 22 per cent; and cholesterol, 272 mg. per cent; the patient was given gradually increasing doses of Tapazole alone, from 40 to 80 mg. per day, for a period of twenty-seven days without detectable change in urinary 5-HI excretion. However, when Lugol's solution, 60 drops per day was added to the Tapazole and given for an additional fourteen days, there was a marked fall in values of 5-HI excretion to an average of 70 mg. per day. At a later point in the study the patient was given Lugol's solution alone, 60 drops daily, and there was a fall in average daily excretion

* The BAS used in this study was supplied by Dr. Frederick K. Heath and Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey.

TABLE II
EFFECT OF DIETARY INTAKE OF FAT UPON THE URINARY EXCRETION OF 5-HI

Dietary Periods	5-HI (mg./24 hr.)	
	Average	Range
High fat (8 days)	131	89–158
Regular (5 days)	119	102–138
High fat (5 days)	139	114–157
Low fat (5 days)	128	92–158
Regular (7 days)	112	89–138

TABLE III
URINARY EXCRETION OF 5-HI DURING ADMINISTRATION OF IPRONIAZID (MARSILID)

Periods	5-HI (mg./24 hr.)	
	Average	Range
Control period I (8 days)	113	89–138
Marsilid, 50–100 mg. daily (27 days)	89	67–116
Control period II (8 days)	116	97–136
Marsilid, 75–150 mg. daily (21 days)	100	59–158
Control period III (8 days)	128	81–183

from 172 mg. to 127 mg. during the twelve days of Lugol's administration. However, this fall in urinary excretion likewise was shown to be due to interference with the chemical reaction. When Lugol's solution 0.2 ml. of 1:200 dilution was added to 0.016 mg. of 5-HIAA, only 11 per cent of the 5-HIAA could be recovered by the chemical method of analysis employed. Addition of the same amount of a 10 per cent solution of potassium iodide resulted in a 77 per cent recovery of 5-HIAA. Therefore, it was specifically the iodine and not the potassium iodide which produced the interference. During the administration of these antithyroid drugs there was no change in cholesterol or basal metabolic rate.

Diet: The patient was given a high fat diet containing 160 gm. fat, 80 gm. protein and 100 gm. carbohydrate for eight days, followed by four days on a regular diet, then a high fat diet for the next five days, followed by a diet containing 30 gm. of fat daily for the next five days. The urinary excretion of 5-HI during the periods of high fat, regular and low fat diets is indicated in Table II. Although the average excretion of 5-HI did increase somewhat on the high fat diet, there was no change in the patient's symptoms. At a later date the patient was given a low protein diet containing 30 gm. protein, 100 gm. fat and 300 gm. carbohydrate for a period of six days. This diet contains approximately 250 mg. of L-tryptophan. During the time she was on this diet there was no significant decrease in excretion of 5-HI.

Iproniazid (Marsilid®): Iproniazid was administered orally 50 to 100 mg. daily for a period of twenty-seven days; then the patient was given no medication for the next eight days; then iproniazid was resumed in increasing doses from 100 to 150 mg. daily for the next twenty-three days. During the period of iproniazid administration there was a marked exacerbation in the patient's diarrhea and facial flushing, both of which symptoms abated when administration of the drug was discontinued. The urinary excretion of 5-HI during the control period and periods of iproniazid administration is indicated in Table III. Neither iproniazid nor its urinary excretion product caused any interference with the chemical determination of 5-HI. There was no change in the patient's reflexes, headache or mental status during the time she received the drug.

COMMENTS

Within the past few years the metabolic pathway of serotonin formation and excretion has been established in detail as well as the physiological role it plays in the clinical picture of the carcinoid syndrome [*1,2,9,10*]. The essential amino acid L-tryptophan, by hydroxylation, forms 5-hydroxytryptophan [*9*]. The latter undergoes decarboxylation to form 5-hydroxytryptamine (5HT), or serotonin. This reaction has been shown *in vitro* to be mediated through a specific enzyme 5-hydroxytryptophan decarboxylase. The 5-hydroxytryptamine undergoes deamination to form 5-hydroxyindoleacetic acid, the excretion product, this reaction being dependent on monoamine oxidase [*11*].

Sjoerdsma et al. have shown that in normal subjects only 1 per cent of ingested tryptophan is converted to serotonin, the rest being available for the formation of niacin and protein. In patients with the carcinoid syndrome as much as 60

per cent of dietary tryptophan may be diverted into the biosynthesis of 5-hydroxytryptamine [*1*].

In the studies herein described it was our purpose to attempt to interfere at various stages with 5-hydroxytryptamine formation, or to alter its physiologic actions. It is to be noted that the study of the metabolic activity of this patient with carcinoid tumor was limited only to clinical observation and measurement of urinary excretion of total 5-HI of which 5-HIAA constitutes approximately 75 per cent. During the period of study there were spontaneous changes in excretion of 5-HI, as evidenced by a fluctuating baseline. Because of this, only marked changes in excretion under therapy can be considered significant.

Tryptophan. Since L-tryptophan is the primary precursor of serotonin, it was of interest to determine the effect of tryptophan loading and depletion. It has been established that the minimal daily requirement of this essential amino acid is 0.25 gm. per day [*12*]. Sjoerdsma et al. [*1*] have pointed out that in normal subjects, since 5-hydroxyindoles account for only a small fraction of ingested tryptophan, it is likely that the usual amount of tryptophan ingested saturates the "5-hydroxyindole formation mechanism." It has been demonstrated in normal volunteer subjects, that over a wide range of tryptophan loading urinary excretion of 5-hydroxyindoles remains essentially unchanged. The administration of 5 to 10 gm. of tryptophan causes only a slight rise in urinary 5-HIAA in normal dogs [*1*].

On the other hand, Sjoerdsma et al. were able to demonstrate that in a patient with carcinoid tumor the urinary excretion of 5-HIAA could be markedly increased by increasing dietary tryptophan to 1,400 and later 3,500 mg. per day [*1*]. This is consistent with the fact that their patient converted 60 per cent of ingested tryptophan to 5-hydroxyindoles and therefore, the patient's system was probably not saturated on a normal diet. Even here, however, the limit of 5-hydroxyindole forming capacity was probably being reached since the absolute increase was not proportional to the tryptophan intake.

In the present studies, intensive tryptophan loading only slightly increased the urinary excretion of 5-HI. This we believe is due to the fact that, unlike the aforementioned patient, the 5-hydroxyindole forming capacity in our patient may be almost completely saturated, even on a normal diet. Absorption of L-tryptophan from the gut does not seem to be a factor because intravenously administered L-tryptophan did not significantly increase urinary excretion of 5-HI.

At a later date in the study, when the patient was given a diet containing 30 gm. of protein and 250 mg. of tryptophan, there was no significant change in urinary excretion of 5-HI. The tumor in this case is apparently able to divert the same amount of ingested tryptophan towards the synthesis of serotonin whether the amount of dietary tryptophan be high or just at the level of the minimum daily requirement.

Chelating Agents and Inhibition of 5-Hydroxytryptophan Decarboxylase. In vitro studies by Beiler and Martin [*13*] have shown that the enzyme system 5-hydroxytryptophan decarboxylase, which is essential for the conversion of 5-hydroxytryptophan to 5HT (serotonin), could be inhibited by certain carbonyl reagents and chelating compounds. They found that the amount of serotonin formed by a guinea pig kidney homogenate incubated with 5-hydroxytryptophan could be inhibited by sodium ethylenediaminetetracetic acid (versene). The latter's inhibitory effect was reversed by the addition of the divalent cations, manganese, magnesium and zinc, which would seem to implicate a divalent metal in this enzyme system.

It occurred to us that this might serve as a means of inhibiting serotonin formation, and thus afford at least symptomatic relief to the patient. However, our studies failed to reveal any *in vivo* inhibitory effect by several chelates on the formation of serotonin as measured by diminution in the excretion of 5-HI.

Attempts to Affect the Release of Serotonin. Histamine: The intimate relationship between histamine and serotonin is well established. It has been demonstrated that damaged mast cells release serotonin as well as histamine, that damaged platelets release both serotonin and histamine, and that in anaphylactic shock serotonin is released into the plasma [*14,15*]. Both of these substances cause edema and hyperemia when injected into the skin of the experimental animal, and serotonin has several other pharmacologic effects very similar to histamine [*16*].

In studies on a patient with metastatic carcinoid tumor reported by Daugherty et al. [*17*], it was found that injection of 0.05 mg. of histamine diphosphate subcutaneously resulted in a substantial rise in blood serotonin and a vasomotor reaction characterized by a salmon red color of the skin which extended to the toes.

The latter was described as different from the usually observed "histamine flush," both qualitatively and quantitatively. Concomitant studies of urinary 5-HIAA were not made.

We were not able to detect any significant rise in urinary 5-HI following intravenous administration of histamine nor did our patient demonstrate the vasomotor reaction described. It is of interest that Waldenstrom and Ljunberg [*2*] were unable to confirm the clinical and laboratory observations noted in the report of Daugherty et al.

Reserpine: Recent reports have shown that reserpine and serotonin have similar physiologic actions, i.e., bronchoconstriction, increased gastrointestinal motility, diarrhea, vasomotor disturbances and potentiation of the sedative effect of hypnotics [*18–20*].

There is evidence to support the concept that at least part of the action of reserpine is mediated through the release of bound serotonin. It has been shown that intravenous administration of reserpine to rabbits depleted brain serotonin by 90 per cent [*21*], that intraperitoneal administration of reserpine to rabbits caused a decrease in concentration of serotonin in segments of the gastrointestinal tract [*22*], and that the daily administration of 1 mg. of reserpine intramuscularly to nine normal human subjects virtually depleted platelets of their serotonin within one week [*23*]. One would therefore expect that reserpine, by releasing bound serotonin, would increase the excretion of the serotonin metabolite, 5-HIAA. The first day reserpine was given orally to our patient, there was a marked rise in urinary 5-HI excretion. Continued administration, however, did not alter the excretion of 5-HI. This initial response followed by subsequent refractoriness is comparable to that noted by Shore et al. in normal dogs [*18*]. They found that when 3 mg. of reserpine per kilogram body weight was given intraperitoneally, urinary 5-HIAA rose markedly for the first eight hours following injection and then dropped to below normal values. On the following day a subsequent dose of reserpine did not increase the excretion of 5-HIAA. The results noted by Shore et al. in normal dogs [*18*] and by us in this patient with metastatic carcinoid suggest that after initial release of serotonin, body stores are depleted so that reserpine is no longer effective in producing serotonin release until the stores can be replenished. It is also possible that reserpine does not produce release from the major body store, e.g., the tumor itself, in a patient with metastatic carcinoid.

Peripheral Antagonists of Serotonin. BAS: Because of the possible role serotonin might play in hypertension, Woolley has synthesized several analogs of serotonin which might act as antimetabolites [*24–26*]. One of these, BAS, benzyl analog of serotonin (1-benzyl 2,5-dimethyl serotonin) has been found by Wilkins to lower the blood pressure in hypertensive patients [*27,28*]. Wilkins and Hollander [*28*] have reported that three carcinoid patients given BAS responded with a decided lessening of the symptoms of facial flushing, abdominal cramps and diarrhea. In another recent report [*29*], a patient with metastatic carcinoid given BAS in doses of 100 to 400 mg. a day for nine days had no decrease in the number of flushes, although the severity of these flushing attacks was slightly diminished. In our patient, no symptomatic improvement was noted and there was some evidence of toxicity as manifested by nausea, vomiting and diarrhea. Since the presumed action of BAS is one of peripheral antagonism to serotonin, it need not influence the rate of excretion of 5-HI, and indeed no such effect was noted.

Chlorpromazine: Considerable evidence has accumulated which establishes chlorpromazine as an antagonist of the peripheral effects of serotonin. In spinal cats the vasopressor effect of 20 to 40 μg./kg. of scrotonin is blocked by 1 mg. of chlorpromazine [*30*]. The stimulatory action of both serotonin and acetyl choline on the colon strip of rats could be inhibited by the addition of chlorpromazine to the bath [*31*]. Pretreatment with intravenously administered chlorpromazine at doses of 1.0 and 2.5 mg./kg. will abolish the local edema caused by injection of serotonin and histamine into a rat's paw [*31*].

Consistent with these effects is our finding that chlorpromazine gave symptomatic relief to our patient, as manifested by improvement in her diarrhea. Similar favorable results were noted in a recent report in which 100 mg. of chlorpromazine were given daily for four days, with exacerbation of diarrhea after administration of the drug was discontinued [*32*].

The administration of chlorpromazine in our case was associated with very low values of urinary 5-HIAA. In a separate study [*33*] we have shown by *in vitro* analysis that this effect is apparent rather than real. The presence of

chlorpromazine or its excretory products inhibits color development in the chemical analysis for 5-HI, thus resulting in a spuriously low value. In addition to chlorpromazine (2-chlor-10-[gamma dimethylamine-n-propyl] phenothiazine), other derivatives of phenothiazine such as compazine (2-chlor-10-3-[1-methyl-4-piperazinyl] propyl phenothiazine), Sparine® (10-[gamma-dimethylamino-n-propyl] phenothiazine), methylene blue (3,6 di-[dimethylamino] phenothiazine) and Phenergan® (10-beta-dimethylamino-n-propyl-phenothiazine), all produce this inhibition of color development. That true excretion of 5-HIAA actually remains unchanged and is merely masked, has been demonstrated by chromatographic technics [*33*]. This is consistent with the evidence for a peripheral antagonism between chlorpromazine and serotonin, since a peripheral antagonist would not be expected to interfere with the formation of serotonin or its excretion as 5-HIAA.

Chlorpromazine therefore appears to be a clinically useful drug for the symptomatic treatment of these patients, but one which may interfere with chemical studies of 5-HI.

Methimazole and Lugol's Solution. An attempt was made in this study to reduce the tumor metabolism by rendering the patient hypothyroid through the use of an antithyroid agent, methimazole (Tapazole). No change in urinary excretion of 5-HI occurred. When Lugol's solution was added there was a decrease in 5-HI excretion as measured by the chemical method. In *in vitro* experiments, however, it was found that the elemental iodine of Lugol's solution causes an interference with the chemical analysis for 5-HIAA, similar to that which occurs with chlorpromazine.

The treatment of the patient with methimazole and Lugol's solution failed to induce hypothyroidism. The production of a hypometabolic state by more vigorous means such as radioactive iodine might be worth a therapeutic trial in an advanced case of carcinoid syndrome.

High Fat Diet. In 1955, Bleehen [*34*] reported on a patient with metastatic argentaffin carcinoma in whom attacks of flushing and diarrhea could be precipitated by a high fat intake. The urinary excretion of 5-HIAA on the day of the high fat diet was more than twice that on a low fat diet. When our patient was given a high fat diet, exacerbation of her symptoms failed to occur although a slight increase in urinary 5-HI excretion was noted.

Monamine Oxidase Inhibition. It has been fairly well established that monamine oxidase is involved in the breakdown of 5-hydroxytryptamine with the production of 5-hydroxyindoleacetic acid, the urinary excretion product [*11*]. It is also known that monamine oxidase activity is found in large amounts in the mitochondria [*35,36*].

Several recent studies have shown that 1-isonicotinyl 2-isopropyl hydrazide, iproniazid (Marsilid), is an effective monamine oxidase inhibitor. This has been demonstrated by the addition of iproniazid to mitochondrial suspensions [*11,35*]. It has also been found that mitochondrial suspensions of rat and guinea pig liver and brain obtained after the intact animal had been injected with iproniazid inhibited monamine oxidase activity [*37*]. Similar results have also been demonstrated in the dog [*11*]. This implies that in the intact animal iproniazid manifests its central nervous system effects through the accumulation of sympathomimetic amines normally inactivated by monamine oxidase. Furthermore, preliminary studies suggest that iproniazid can potentiate the effects of serotonin *in vivo*. When rats were pretreated with iproniazid there resulted a reddish blue discoloration of the tail, decreased skin temperature of the hind legs and marked tranquilization lasting for three hours after the intraperitoneal injection of 3 mg. of serotonin [*11*]. In control animals not given iproniazid the effects of injected serotonin were not discernible.

We were therefore interested in the effect of iproniazid on our patient with metastatic carcinoid tumor. If effective monamine oxidase inhibition occurs, then urinary excretion of 5-HIAA should fall due to decreased formation from serotonin. Likewise, the effective levels of endogenous serotonin should be elevated with resultant exacerbation of the patient's symptoms. This latter effect was quite prominent in our patient, marked flushing and diarrhea occurring on administration of iproniazid. Urinary 5-HI excretion decreased approximately 20 per cent during the period of drug administration. Moreover, when the iproniazid administration was discontinued the patient's symptoms subsided and her urinary excretion of 5-HI rose to previous levels.

SUMMARY AND CONCLUSIONS

A case study of a patient with metastatic carcinoid is presented. In the 336 days the pa-

tient has been followed up, her average twenty-four hour urinary excretion of total 5-hydroxyindoles (5-HI) increased from 94 to 166 mg.

Oral tryptophan loading caused a slight increase in 5-HI excretion. Several chelating agents given intravenously had no effect on 5-HI excretion. Relatively high doses of intravenously administered histamine failed to exacerbate the patient's symptomatology or to affect 5-HI excretion. Reserpine, given orally, produced an initial but unsustained rise in 5-HI excretion and an exacerbation of the patient's diarrhea throughout the period of administration. BAS failed to influence urinary 5-HI excretion and was associated with mild gastrointestinal disturbances. Amelioration of diarrhea by the administration of chlorpromazine was confirmed, but the decrease in 5-HI excretion with this drug was found to be spurious due to interference with color development in the chemical analysis for 5-HI. Lugol's solution also produced this type of chemical interference. A high fat diet failed to produce an exacerbation of the patient's symptoms although the urinary excretion of 5-HI was slightly increased. Iproniazid produced a marked increase in diarrhea and facial flushing with a concomitant decrease in 5-HI excretion.

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Massive Edema Due to Bilateral Incomplete Renal Artery Occlusion

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Occlusion of the renal artery has been well described as it occurs in its typical form [*1,2*]. The symptoms include pain in the flank, hypertension, hematuria, oliguria and uremia. The renal artery occlusion may be due to either emboli or thrombi and is frequently associated with renal infarction. Cases are often complicated by pre-existing cardiovascular disease. The diseased heart serves as a source of emboli to the renal arteries, and is the apparent cause of the edema found in many of these cases.

Partial occlusion of a renal artery in the laboratory animal produces a retention of sodium and water [*3–5*]. The following case report is that of massive edema associated with thrombosis of the renal arteries without evidence of heart disease. It is postulated that the mechanism of salt and water retention in this case is analogous to that observed in experimental renal artery constriction.

CASE REPORT

A thirty-eight year old white male house painter was admitted to the Denver Veterans Administration Hospital on September 26, 1953. He had an intermittent pressure-type pain in the epigastrium of ten days' duration which was not relieved by food or alkali. During the week prior to admission he also noted intermittent swelling of his abdomen and had a very poor appetite but no nausea or vomiting. His urine had a dark color, and he had had some diarrhea. Two days prior to admission there was swelling of the legs and ankles.

The past history was not contributory; the patient considered himself to have been in very good health until ten days prior to admission.

On admission to the hospital the patient was noted to be asthenic, slightly icteric, acutely ill and somewhat confused. The temperature was 98.6°F., pulse 96, respirations 20, and blood pressure 170/94 mm. Hg. There was no cardiomegaly. A grade 2 systolic murmur was heard at the apex. Moist rales were heard throughout both lung bases posteriorly. The liver edge was palpable 8 cm. below the right costal margin. The most remarkable finding was the presence of massive edema of the extremities. The pitting edema extended as high as the nipple line and considerable ascites were present.

Laboratory studies during the first week of hospitalization revealed the following: The white cell count was 13,200 per cu. mm. with a normal differential; hemoglobin, 13 gm. per cent and hematocrit, 44 per cent; sedimentation rate, 22 mm. per hour; and serologic test for syphilis (VDRL), non-reactive. Urinalysis revealed a specific gravity of 1.022; 1-plus albumin; 10 to 20 white blood cells per high power field; and a negative test for sugar. Subsequent urine specimens occasionally showed casts and numerous red blood cells (after the insertion of an indwelling catheter). Although the serum bilirubin on September 28, 1953, was elevated to 4.0 mg. per cent, other liver function studies revealed no abnormalities.

During the early part of the patient's hospital course it was noted that he had a low twenty-four hour urinary output. On September 29, 1953, the venous pressure in the antecubital vein was 160 mm. of water and the edema was increasing. Because of a serum sodium level of 125 mEq. per L., an infusion of hypertonic saline solution was given. The latter resulted in an increased urinary output only during the infusion, and the net result was a further gain in weight. X-ray examination of the chest on September 30, 1953, revealed moderate dilatation of the heart and congestion of the lung fields. (Figs. 1 and 2.)

On October 5, 1953, a diastolic gallop rhythm was noted. At this time the patient's weight was 160 pounds. After digitalization the gallop rhythm disappeared. An electrocardiogram taken at this time was considered abnormal. (Fig. 3.) Subsequently, diuresis occurred for a short period, only to be followed by a recurrence of oliguria. This pattern characterized the subsequent course of four and a half months. Despite efforts at diuresis which included mercurials, ammonium chloride, aminophylline, paracentesis, Southey tubes, and a low sodium diet (2.5 gm.), he continued to show anasarca and hypervolemia with

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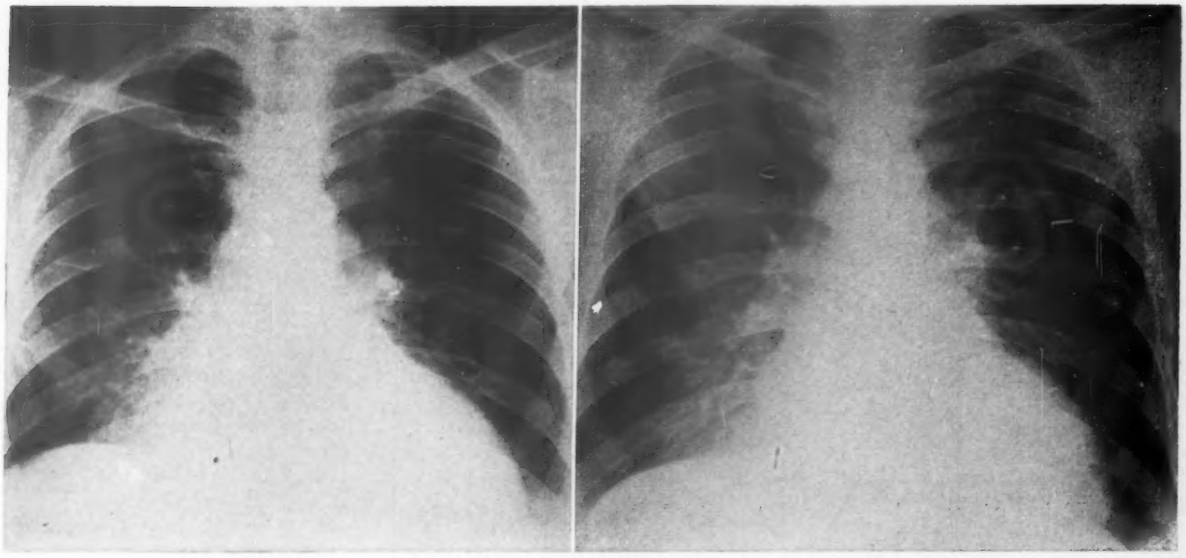

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FIGS. 1 and 2. Chest x-rays taken on September 30, 1953 (Fig. 1) and on October 21, 1953 (Fig. 2). Both show dilatation of the heart and moderate congestion of the lung fields.

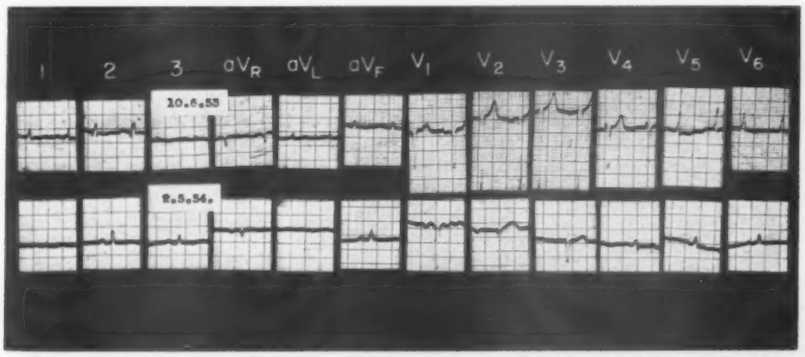

FIG. 3. Electrocardiograms taken on October 6, 1953 and on February 5, 1954.

hyponatremia. A consistent finding was the virtual lack of sodium excretion in the urine. The pattern of weight and electrolyte balance is given in Table 1. The hemoglobin and white blood count did not vary significantly throughout the patient's hospital course. The serum proteins were 5.2 gm. per cent on admission and remained above 5.0 gm. per cent on all subsequent determinations. The blood cholesterol was 170 mg. per cent. The blood volume on December 17, 1953, measured by means of I^{131} tagged albumin was 4.8 L. or 90 cc. per kg. of body weight.

By October 14, 1953, a soft blowing grade 2 aortic diastolic murmur was noted along the left sternal border. The aortic first and second sounds were intact. The blood pressure was 204/76 mm. Hg. The murmur was heard intermittently by October 19, 1953, and the blood pressure was 160/92 mm. Hg. After the twenty-third of the month the murmur was no longer audible. On October 26, 1953, a diastolic gallop was again heard intermittently. X-rays continued to show an increase in the size of the cardiac silhouette.

The patient's course was one of gradual deterioration. He remained a problem of intractable edema and ascites. He was noted to have spontaneous diureses on several occasions, usually following a paracentesis. He continued to show evidence of renal damage, with 1 to 3-plus albuminuria and numerous red and white cells in the urine. His urea clearance on October 14, 1953, was 61 per cent and on October 26, 1953, 70 per cent. Nitrogen retention or acidosis was never a problem, although a moderate increase in the blood urea nitrogen occurred terminally. The blood urea nitrogen on February 2, 1954, was 35 mg. per cent and increased to 68 mg. per cent by February 9, 1954. Other than the elevated serum bilirubin associated with bromsulfalein retention and hepatomegaly, tests of hepatocellular function remained normal. Biopsies of the liver, bone marrow and skin did not contribute to the diagnosis.

He demonstrated progressive muscle wasting associated with increasing weakness. An area of blue-black discoloration appeared on the right great toe

TABLE I

PERTINENT WEIGHT AND ELECTROLYTE DATA

Hospital Days	Weight (lb.)*	Urine Electrolytes (mEq./L. per 24 hr.)†			Serum Electrolytes (mEq./L.)†				Blood Urea Nitrogen	Comments
		Na	Cl	K	Na	Cl	K	CO_2		
1 to 5	155	...	....	..	125	88	4	27	22	5 per cent NaCl, NH_4Cl
6 to 12	167	...	24.7	..	124	93	5.3	21	22	Intravenous albumin, Hg diuretics
13 to 19	135	4	56	74	120	98	6.6	....	23	Weight loss due to Southey tubes
20 to 26	120	<3	35	45	132	90	5	....	31	Paracentesis
27 to 33	132	<3	34	27	134	...	4.7	20	18	.....
34 to 40	120	<2	....	30	128	97	...	18	..	Paracentesis
41 to 47	106	4	40	74	124	100	4	14	..	Hg diuretics
48 to 54	120	5	12	14	...	...	...	....	..	Weight gain despite Hg diuretics
55 to 61	113	5	36	49	...	...	...	....	..	Hg diuretics
62 to 68	124	5	18	31	...	...	...	....	..	Hg diuretics
69 to 75	127	13	39	58	...	...	...	....	..	Hg diuretics
76 to 82	107	...	....	..	136	91	3.4	....	..	"Primed" with NH_4Cl prior to mercurials
83 to 89	100	...	....	..	114	75	3	....	..	.....
90 to 96	109	<5	10	26	120	85	3.7	....	..	Edema persisting despite diuretics
97 to 103	102	<5	20	21	120	81	4.8	....	23	.....
104 to 110	107	...	....	..	125	75	3.8	20	..	5 per cent NaCl with resulting weight gain
111 to 117	95	...	....	..	125	91	4.2	24.4	..	.....
118 to 141	105	...	....	..	132	105	5.7	12	68	General muscle wasting persistent ascites, edema
142	...	...	....	..	...	...	...	....	..	Died

* The weight recorded represents that found at the end of the time period.

† Urinary and serum electrolytes represent one determination obtained during the indicated period of time.

without sharp demarcation. Hemorrhagic blebs developed terminally around both knees, and decubitus ulcers appeared on the posterior and lateral aspects of the hips. After several weeks of a terminal appearance, the patient died on February 13, 1954.

At autopsy the significant postmortem findings were as follows: The left pleural cavity contained 2,500 cc. of a clear straw-colored fluid. The right chest contained 200 cc. of fluid. Approximately 500 cc. of clear yellow fluid was present in the peritoneal cavity. The left lung was completely atelectatic and lay against the hilum. The right lung appeared to be well aerated with the exception of the posterior inferior portion which was congested. Microscopically the lungs showed marked chronic, passive congestion.

The transverse pericardial diameter was 14 cm. and the heart weight was within normal range. The pericardium contained approximately 20 cc. of clear straw-colored fluid. The valves were normal and competent. The tricuspid valve measured 12.5 cm., mitral 8.5 cm., pulmonary and aortic 7.0 cm. The right and left ventricles were moderately dilated and no intracardiac thrombi were noted. The coronary vessels were patent throughout, and had a minimal amount of sclerotic change. The ascending aorta measured 7 cm. in circumference and there was some longitudinal wrinkling and a moderate amount of atherosclerotic change. On microscopic examination the left myocardium showed fibers which were slightly thicker than normal. There were scattered focal scars composed of loose areolar fibrous tissue in which occasional hemosiderin macrophages and rich vascularization were noted. The right ventricle showed no remarkable features.

The liver weighed 1,100 gm. and was smooth with a light brown color. The cut surface was smooth with indistinct lobular pattern. On microscopic examination the only finding of note was marked chronic passive congestion. The gallbladder, spleen, pancreas, adrenals and bowels were normal both grossly and microscopically.

The right kidney weighed 190 gm. The capsule

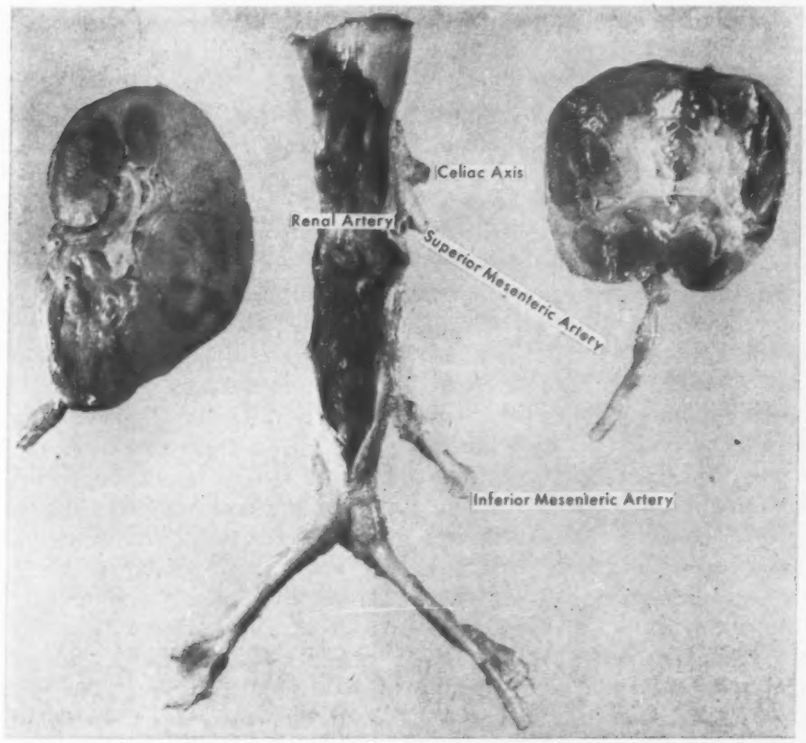

FIG. 4. Photograph showing the thrombus in the abdominal aorta and cut surfaces of the kidneys.

stripped readily revealing a smooth, pale yellow-red surface. On section the medulla and cortex were easily outlined. The average thickness of the cortex was approximately 7 mm. The left kidney weighed 50 gm. The capsule stripped with difficulty. There was a circumscribed raised yellow area of infarction occupying most of the lower third. (Fig. 4.) On section the medullary and cortical portions were easily discernible; the cortex measured approximately 4 mm. in thickness. The ureters, bladder and prostate appeared normal.

On microscopic examination the left kidney showed generally altered architecture. The glomeruli were slightly larger and more cellular than usual with increased prominence of endothelial cells and occasional neutrophils. There was considerable increase in interstitial fibrous tissue throughout with corresponding diffuse atrophy of all tubules. There were foci of complete fibrous obliteration of the glomerular tufts, this being especially marked along the margin of an area of coagulation necrosis corresponding to the infarct described grossly. The vessels were of moderately increased prominence, due more to surrounding atrophy than to actual sclerotic change. Section of the right kidney showed a well marked increase in glomerular size which appeared to be due to endothelial proliferation. The tubular pattern was intact throughout and the tubular epithelium did not appear to be significantly altered.

The abdominal aorta was very firm. Upon opening, it was found to contain a thrombus reaching from approximately 2 cm. above the celiac axis and extending down into the internal iliac vessels on both sides. (Fig. 4.) The orifice of the left renal artery was completely occluded. The orifice of the right renal artery was only partially occluded. A channel less than 1 cm. in diameter was present along the right lateral wall of the aorta allowing access of a moderate amount of blood. The inferior mesenteric artery was bound down with adhesions to the lateral aspect of the aorta and the lumen was apparently obliterated. Below the level of the right renal artery, occlusion of the lumen of the aorta was complete. Section of both iliac arteries revealed complete occlusion by firm yellow-white organized thrombi. The inferior vena cava and renal veins were free of thrombi.

The pathological diagnoses were the following: (1) Aortic thrombosis extending from the celiac axis to involve the common iliac arteries, with complete occlusion of the left renal artery and partial occlusion of the right renal artery. (2) Minimal cardiac dilatation and marked chronic passive congestion of lungs and liver. (3) Severe atrophy and infarction of left kidney.

COMMENTS

A case is presented manifesting refractory massive edema and ascites of five months'

duration, compatible with a primary renal inability to excrete sodium. Pathologically, the primary lesion was found to be a massive thrombus of the renal arteries with infarction and atrophy of one kidney and evidence of chronic ischemia of the other. The remainder of the findings at autopsy can be explained by the hypervolemia and congestion the patient demonstrated during the last five months of life. The cardiac murmurs suggesting aortic and mitral insufficiency and the diastolic gallop appeared during the episodes of most marked hypervolemia and disappeared with diuresis. The absence of demonstrable valvular or myocardial lesions at autopsy confirms the clinical impression that these murmurs were of functional origin. In spite of the many clinical findings suggestive of congestive heart failure there was no pathological evidence that the patient had any organic heart disease. The impaired blood supply to the lower extremities was not apparent except terminally and did not seem to be a significant factor in the patient's course; the collateral circulation apparently being adequate during most of the observed illness. In retrospect the epigastric pain and icterus observed during the early course of the illness can be attributed to the massive thrombosis with infarction of tissue. Indeed, the vague pain associated with oliguria at the onset of the patient's illness was the only feature common to the usual clinical description of renal artery thrombosis. The subsequent course was simply a problem of impaired sodium excretion associated with fluid retention and the development of the classical picture of congestive failure with concomitant congestive changes in the viscera.

The clinical and pathological picture presented by this case is a unique reproduction of the experiments of Mueller [*3*], Pitts [*5*] and Blake [*4*]. Mueller [*3*] observed that constriction of the renal artery in the dog resulted in a reduction in sodium and water output varying with the degree of constriction. Following slight constriction of one renal artery, the sodium and water output of the ligated side is permanently (four to six weeks) reduced to 20 to 50 per cent of the unligated side, without a detectable decrease in the renal plasma flow and glomerular filtration. With greater constriction of one renal artery and a detectable reduction in renal plasma flow and glomerular filtration of 20 to 30 per cent, the excretion of salt and water fell to only a few per cent of the unligated kidney. The total excretion of sodium remained adequate due to an increase by the unligated kidney. Pitts [*5*] noted that in dogs a moderate reduction in the filtration rate greatly restricted the capacity of the kidney to eliminate water and salt when the aorta was constricted above the renal arteries, and attributed the failure of action of mercurial diuretics to a relative lack of sodium presented to the distal segment of the tubules because of nearly complete absorption in the proximal segment. Merrill [*6*] has shown that in congestive heart failure there is a decreased glomerular filtration rate associated with a relatively greater reduction in renal plasma flow, and inferred that the sodium retention in congestive heart failure is due to a reduced filtration of sodium without a concomitant reduction in the tubular sodium reabsorptive capacity.

The patient presented the classical picture of congestive failure due to marked retention of sodium and water with a normal heart. The primary fault was a marked reduction in renal blood flow and glomerular filtration, secondary to the complete thrombosis of the left renal artery and marked reduction of the caliber of the right renal artery. A glomerulotubular imbalance resulted in which there was a reduction of glomerular filtration without an equivalent reduction in the tubular reabsorptive capacity for sodium and water. This has been amply demonstrated in experimental animals by Mueller [*3*], Pitts [*5*] and Blake [*4*]. The relative disproportion in the tubular reabsorption of sodium has been attributed by Luetscher [*7*] to an increased aldosterone output, and in this case may account for the relatively large amounts of potassium excreted. It is possible that the sodium and water retention was initiated by means of as yet unidentified "volume receptors" responding to an inadequate filling of some portion of the arterial tree distal to the thrombosis [*8*].

Although certainly in congestive failure the inadequacy of the circulation is the initiating factor, it is the alteration in renal function, secondarily affected, that is ultimately responsible for the accumulation of excess sodium and water in the body. However, in this particular patient (with a normal heart) the picture of congestive failure (of such severity as to lead to death) was exhibited but the primary fault was occlusive disease of the renal arteries. Thus it would seem that reduced excretion of sodium, irrespective of cause, leads to expansion of the

extracellular stores of salt and water and accumulation of edema with the clinical picture of congestive heart failure. This case, then, demonstrates how a primary renal fault can produce the entire picture of congestive failure.

Others have described cases in which hypervolemia and congestive failure were associated with renal artery thrombosis but these cases have invariably had serious pre-existing cardiac lesions and were characterized by hypertension, renal excretory failure and, frequently, death [*2*].

The relatively normal blood urea nitrogen and urea clearance manifested by this patient during all but the terminal stages of his disease can be explained on the basis of the small vascular channel leading to the right kidney. This narrow channel was sufficient to maintain an adequate renal function for the excretion of urea but not of salt and water. Reduced excretion of water and sodium have been noted by both Mueller [*3*] and Blake [*4*] to occur without measurable change in renal plasma flow and glomerular filtration rate when slight constriction of a renal artery was used. This mechanism would allow normal nitrogen excretion in the face of simultaneous salt and water retention and explain the normal blood urea nitrogen maintained throughout most of this patient's illness. Indeed, the urea clearances in the first month of this patient's illness were 71 and 70 per cent of normal.

SUMMARY

The case herein presented, of bilateral incomplete renal artery occlusion, demonstrates chronic sodium retention in the absence of cardiac disease; normal nitrogen excretion during most of the course of the illness; and an associated primary "constriction" of the blood supply to the renal arteries, thus reproducing in general the findings usually obtained in the experimental animal after renal artery constriction. There resulted a refractory massive edema and ascites of five months' duration, terminating in death. The urinary excretion of sodium was extremely small throughout the hospital course despite all therapeutic measures. At autopsy, a thrombosis of the aorta was noted extending from the internal iliac vessels to the celiac axis. The left renal artery was completely occluded while the blood supply to the right kidney was much reduced.

It is postulated that the sodium and water retention in this case was due to the severe obliterative disease of the renal arteries, and was analogous to that seen in the experimental animal following renal artery constriction. Although the classical picture of congestive heart failure was demonstrated in this patient, the heart at postmortem examination was considered to be entirely normal. Hypervolemia, increased venous pressure, cardiac dilatation, hepatomegaly, murmurs and gallop rhythm all developed, and are ascribable to the effect of the renal artery thrombosis on sodium and water retention.

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Renal Tubular Acidosis with Nephrocalcinosis, Complicated by Hyperemesis Gravidarum*

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HYPERCHLOREMIC renal acidosis with nephrocalcinosis, complicated by hyperemesis gravidarum, makes an interesting combination of clinical and electrolyte disturbances. The following case illustrates the findings in such a situation.

CASE REPORT

H. R., a twenty-three year old housewife complaining of profound muscular weakness, was first seen by me on November 2, 1956. She had had severe vomiting associated with pregnancy on about October 22, and a week later, because of weakness, she had consulted her family physician. He had admitted her to St. Mary's Hospital, Watertown, Wisconsin. The weakness had first involved her legs and had gradually become generalized.

Physical examination revealed a thin, undernourished white woman in whom very marked weakness of all the muscles of her body had developed. This had progressed to the extent of impending respiratory paralysis. The head and neck were normal, except for the spoken voice which was characterized by a nasal twang. The lung fields, heart and abdomen were normal. The blood pressure was 100/60 mm. Hg. Pelvic examination revealed probable pregnancy. An electrocardiogram showed changes compatible with potassium depletion. A serum potassium level was found to be low and potassium chloride was given intravenously. There was no progression of the weakness and two days later there was a striking clinical remission. She was able to use her extremities although they did not have their full strength. Recovery was complete in ten days with intravenous administration of potassium and later oral feeding without supplementary potassium. Emesis ceased. Seven and a half months later a healthy baby boy was born. The labor was normal with the exception of a slightly prolonged second stage.

The patient stated that she had been totally edentulous since the age of seventeen. She had an episode of probable left renal colic at age twenty-one and she had had "stomach trouble" since girlhood. Polydipsia and polyuria had been present as long as she could remember.

The initial serum potassium was 1 mEq./L. and after clinical recovery it was 2.2 mEq./L. Subsequent determinations pre- and postpartum were between 2.9 and 4.4 mEq./L. without administration of extra potassium salts. The initial carbon dioxide combining power was 13 mEq./L. and thereafter remained between 12.5 and 15 mEq./L. The initial serum chloride was 89 mEq./L. The complete blood count was normal. The results of other biochemical and urine studies are summarized in Tables I and II. The electrocardiogram reverted almost to normal after therapy.

Following delivery a radiographic survey of the skeletal system was obtained which failed to reveal any abnormality. A roentgenogram of the abdomen taken with the patient in a supine position showed a diffuse nephrocalcinosis most pronounced in the left

TABLE I
RESULTS OF SERUM ANALYSES, CASE H. R.

Sodium (mEq./L.)	146, 143
Calcium (mg. %)	10.1, 10.8
Fasting blood sugar, (mg. %)	114, 76
Phosphate (mg. %)	1.6
Albumin (gm. %)	2.8
Globulin (gm. %)	2.3
Alkaline phosphatase (King-Armstrong units/100 cc.)	6.8
Uric acid (mg. %)	1.9

NOTE: All values were obtained in the last half of 1956 or first half of 1957, during the patient's pregnancy.

TABLE II
RESULTS OF URINE EXAMINATIONS, CASE H. R.

Urine specific gravity	1.004 to 1.012
Urine pH	7.0 to 8.0
Proteinuria	1 plus to 3 plus
Glycosuria	All specimens were negative
Acetonuria	All specimens were negative
White blood cells in sediment	Few to 7 to 10/h. p. f.
Red blood cells in sediment	All specimens were negative

NOTE: Five specimens taken during pregnancy.

* From St. Mary's Hospital, Watertown, Wisconsin.

kidney. (Fig. 1.) It is interesting to note that an intravenous pyelogram taken two years previously had indicated impaired left renal function without any evidence of calcium deposition in the renal tissue.

It was not realized that she had renal acidosis until after pregnancy and no attempts were made to correct the acidosis. Calcium salts were given in an average amount for pregnancy (150 mg. each day). On September 3, 1957, while receiving sodium bicarbonate (1 gm. each day), the serum carbon dioxide was 20 mEq./L. and the serum chloride was 114 mEq./L.

Because of the frequent familial occurrence of renal acidosis [*7*] the patient's parents, three sisters and one brother were studied. The serum levels of carbon dioxide and chloride were determined. In addition, abdominal films were taken. All the results were within normal limits. One sister, E. H., age twenty-seven years, had lost all her teeth in the year prior to this report. The father, who has diabetes mellitus, gave a history of polydipsia and polyuria. With these exceptions the family history was negative. The patient's child is normal.

COMMENTS

This patient's illness presents several interesting considerations. Hypokalemia has been reported in association with hyperemesis gravidarum [*2*]. Clinically, the patient presented typical symptoms and signs of hypokalemia. Her response to potassium therapy and her general clinical course resembled that seen in previously reported cases of hypokalemia with or without hyperemesis gravidarum. She exhibited, however, a metabolic acidosis instead of the anticipated alkalosis and only a slight depression of serum chloride in place of the expected severe hypochloremia. The serum potassium level was profoundly depressed on admission. No significant distress was observed in conjunction with subnormal serum potassium levels noted on several other occasions. Her electrocardiogram also was almost normal in the presence of distinctly subnormal serum levels of potassium. It would seem likely that the patient is acclimated to a degree of hypokalemia. The patient's clinical status, however, was paralleled by the electrocardiogram and profoundly depressed serum potassium levels were reflected in electrocardiographic abnormalities. It is well known that acidosis will, to a limited degree, protect a patient from the effects of hypokalemia and some of this protection may have been lost by the repeated emesis at the onset of her present illness [*4*]. This was not confirmed by the serum carbon dioxide levels, however. Because of the unexpected acidosis in hyperemesis gravidarum and the tolerance to subnormal levels of potassium, the underlying basis was sought and eventually found.

FIG. 1. Roentgenogram showing nephrocalcinosis.

The supplementary calcium customarily prescribed during gestation undoubtedly contributed to the nephrocalcinosis. The patient is now receiving sodium bicarbonate and potassium bicarbonate, the dosage being adjusted by following her serum levels of carbon dioxide combining power and potassium. The problem is to avoid demineralization without risking deposition of additional calcium within the renal parenchyma [*6*].

The fundamental defect of physiological significance illustrated here lies in the kidney's inability to excrete an acid urine in the presence of systemic acidosis. It is reasonable to assume that the other abnormalities discussed, except the hyperchloremia, could follow as a direct consequence of this failure [*1,5*].

The etiology of hyperchloremic renal acidosis is unknown but it may well be a hereditary defect, particularly as the condition may be related to other disorders of the renal tubule, including the Fanconi syndrome [*8*]. The fact that the patient's immediate family is normal at this time does not of course mean that a similar metabolic derangement may not make its appearance later or may have involved grandparents or other members of the family now deceased.

SUMMARY

A case of a young woman who had renal tubular acidosis with nephrocalcinosis, and in

whom marked hypokalemia developed following hyperemesis gravidarum, is presented and discussed.

Acknowledgment: I would like to thank Dr. Eugene P. Schuh for his permission to follow up the patient, and both Dr. Schuh and Dr. A. C. Nickels for permission to study the members of the patient's family. The Sisters of the Servants of the Holy Ghost at St. Mary's Hospital were very cooperative with laboratory and roentgenographic studies.

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Development of Hemochromatosis in a Patient with Laennec's Cirrhosis*

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IDIOPATHIC hemochromatosis is believed by most investigators to result from a congenital defect [*1,6*] which may permit excessive absorption and deposition of iron in body tissues, with resulting damage to various organs [*2–4*]. The association of Laennec's cirrhosis with hemochromatosis has frequently been noted [*1–5,6*], but a causal relationship between these diseases has not been established [*2*]. The following is a report of a patient with proved Laennec's cirrhosis without hemochromatosis who underwent a portacaval shunt for bleeding esophageal varices and in whom, in the ensuing three years, frank hemochromatosis developed.

CASE REPORT

A fifty year old white male bartender first entered the hospital on August 24, 1952 with a history of marked weakness and massive hematemesis six weeks and again one day prior to admission. He had consumed at least one pint of whiskey daily for over six years, but except for occasional episodes of burning and gnawing epigastric pain following a bout of drinking, denied any previous gastrointestinal symptoms. His food intake had been poor over an indeterminate period. He had suffered an attack of pneumonia in 1941 but had made an apparently uneventful recovery without complications. The family history was non-contributory. Other than as described, his history, past and present, was non-contributory.

Physically, the patient was a well developed but weak and pale individual. His tongue was dry and his skin had lost its normal turgor. There were several "spider" angiomas over the anterior chest wall. His heart was not enlarged to percussion but a grade 2 (grades 1 to 4) apical systolic murmur was heard which radiated to the left axilla. The abdomen was soft, and a firm and rounded non-tender liver edge was palpated 6 cm. below the right costal margin in the mid-clavicular line. No other organs or masses were felt. Peristalsis was active.

The hemoglobin was 4.2 gm. per cent; hematocrit, 17 per cent; leukocyte count, 11,600 per cu. mm. with 68 per cent polymorphonuclears, 32 per cent lymphocytes. The urine was normal. The stool showed gross melena. The serum bilirubin was 1.92 mg. per cent with 1.13 mg. per cent direct-reacting pigment, the prothrombin time was fifteen seconds (control: fourteen seconds), bleeding and coagulation times were normal. A roentgenogram of the chest was within normal limits. Roentgenograms of the upper gastrointestinal tract were suggestive but not diagnostic of esophageal varices. Subsequent studies showed a cephalin flocculation test, 3 plus at twenty-four hours and 4 plus at forty-eight hours; thymol turbidity test, 17.5 units; thymol flocculation test, 1 plus; serum albumin, 3.3 gm.; serum globulin, 4.1 gm.; serologic test for syphilis, negative; blood urea nitrogen, 16 mg. per cent.

Shortly after admission a Sengstaken tube was passed and left in place for thirty-six hours. The patient received 3,000 cc. of whole blood during this period, with a rise in hemoglobin to 12 gm. per cent and in hematocrit to 37 per cent. After removal of the tube further bleeding did not occur. Over the next several weeks the patient received a high calorie, high protein diet and his hemoglobin gradually rose to 13.4 gm. per cent, his hematocrit to 44 per cent, while his serum bilirubin returned to normal. Gastroscopy on September 3, and an esophagram and upper gastrointestinal series on September 10, 1952 were interpreted as normal. Esophagoscopy one week later showed varices involving the distal third of the esophagus.

On December 1 the patient underwent an end-to-side anastomosis of the portal vein to the inferior vena cava. Portal pressures measured directly during surgery were 426 and 194 mm. of water, respectively before and after the shunting procedure. The intra-abdominal findings were within normal limits except for the liver, which was enlarged and appeared cirrhotic, and the collateral venous circulation, which was dilated and distended. The microscopic findings on a 2 by 2 by 1.5 cm. liver biopsy specimen taken at surgery are shown in Figure 1. Active Laennec's cirrhosis with foci of

* From Gastroenterology Section, Wadsworth General Hospital, V. A. Center, and Department of Medicine, University of California Medical Center, Los Angeles, California.

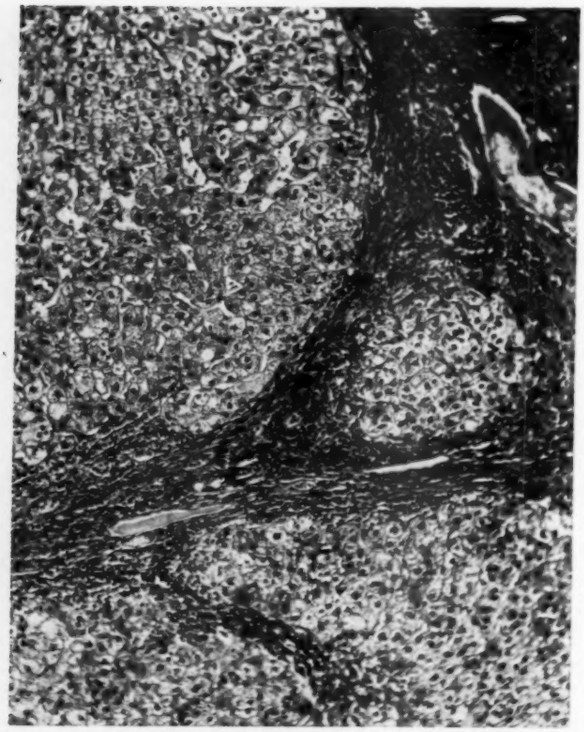

FIG. 1. Section of surgical liver biopsy specimen (December 1, 1952). The normal hepatic architecture is destroyed. Thick, fibrous septums containing proliferating bile ducts and inflammatory cells separate areas of hepatic cell nodular regeneration and necrosis. No hemosiderin is present. Prussian Blue stain.

nodular hepatocellular regeneration, chronic "triaditis," and fairly severe fibrosis were present. Prussian Blue staining failed to show any evidence of hemosiderin deposition.

The patient received 1,500 cc of whole blood during surgery, and a week later, his hemoglobin was 13.0 gm. per cent and hematocrit 39 per cent. He was essentially asymptomatic at the time of his discharge on January 7, 1953.

During the next twenty-seven months the patient was seen at frequent intervals. He complained primarily of recurrent malaise, easy fatiguability and swelling of the ankles. He was advised to adhere to a high protein, high calorie diet and was given vitamins. To the best of the examiners' knowledge he followed these recommendations, and indulged in only one "drinking spree." However, his liver function tests remained abnormal, and his prothrombin time gradually became increasingly prolonged. In March, 1955, the patient left the city.

In July of the same year he experienced the gradual onset of polydipsia and polyuria accompanied, over the next four months, by a 20 pound loss in weight. He did not seek medical attention for these complaints until, in November of the same year, he was admitted to another hospital in a semi-stuporous condition. He was febrile, mildly icteric and dehydrated. His skin color was observed to be slate grey. A film of the chest showed an infiltration in the right lower lobe. The blood sugar was 325 mg. per cent; non-protein nitrogen, 49 mg. per cent; serum albumin, 2.0 gm.; serum globulin, 3.4 gm.; and liver function tests were grossly abnormal. He was treated with antibiotics, insulin and parenteral fluids and made a gradual recovery. At the time of his discharge he was taking 75 units of NPH and 15 units of regular insulin daily.

He was readmitted to this hospital on February 17, 1956 for further evaluation. He still complained of weakness and fatiguability but was otherwise alert and cooperative. Although he had regained 8 pounds in weight since he had started taking insulin, he appeared chronically ill and mildly undernourished. His skin was now slate grey in color, and additional "spider" angiomas were noted over the thorax. His liver was hard, and the lower edge was felt 6 cm. below the right costal margin in the mid-clavicular line. There was pitting edema of the lower extremities extending upward to the knees.

Laboratory studies made on admission showed the urine and leukocyte count to be normal; hemoglobin, 14.2 gm. per cent; hematocrit, 47 per cent; normal bleeding and coagulation times; prothrombin time, twenty seconds (control: thirteen seconds); normal prothrombin consumption time; total cholesterol, 141 mg. per cent with 66 per cent esters; serum albumin, 2.3 gm. per cent; serum globulin, 4.0 gm. per cent; serum bilirubin, 4.48 mg. per cent with 3.44 mg. per cent direct reacting; serum iron, 330 μg. per cent; unsaturated iron-binding capacity, 100 μg. per cent; thymol turbidity test, 18.5; thymol flocculation test, 2 plus; and cephalin flocculation test, 2 plus at twenty-four hours, 3 plus at forty-eight hours. An electrocardiogram showed changes compatible with cor pulmonale.

Throughout his terminal illness the patient remained under good diabetic control on the previously described insulin dosage. However, clinically he pursued a relentless downhill course, manifesting evidence of increasing hepatic decompensation. Despite the discontinuance of all protein and the administration of large doses of arginine and antibiotics, the patient died in hepatic coma on May 11, 1956.

Autopsy findings included moderate dilatation of the right ventricle with some thickening of its wall. There was a small area of leukoplakia but no varices were visible over the distal third of the esophagus. The liver weighed 2,330 gm. and was nodular and hard. The gallbladder and biliary tracts were normal. The spleen weighed 450 gm., and there were areas of soft, dark red degeneration throughout its substance. The portacaval anastomosis was patent.

Microscopically, there were small areas of focal atelectasis in both lungs containing large histiocytes

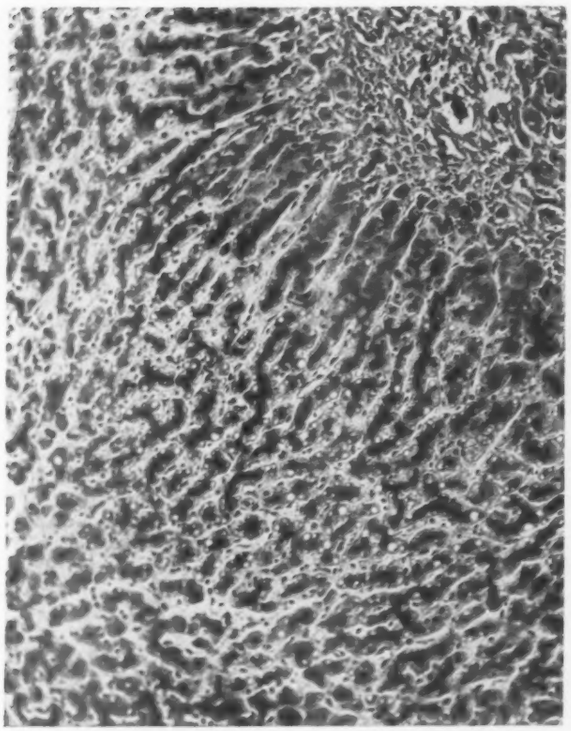

FIG. 2. Liver (May 11, 1956). Prominent fibrosis and nodular regeneration are present. Hemosiderin pigment, which appears black in the photomicrograph, is abundant in the hepatic cells and, to a lesser extent, in the Kupffer cells and connective tissue. Prussian Blue stain.

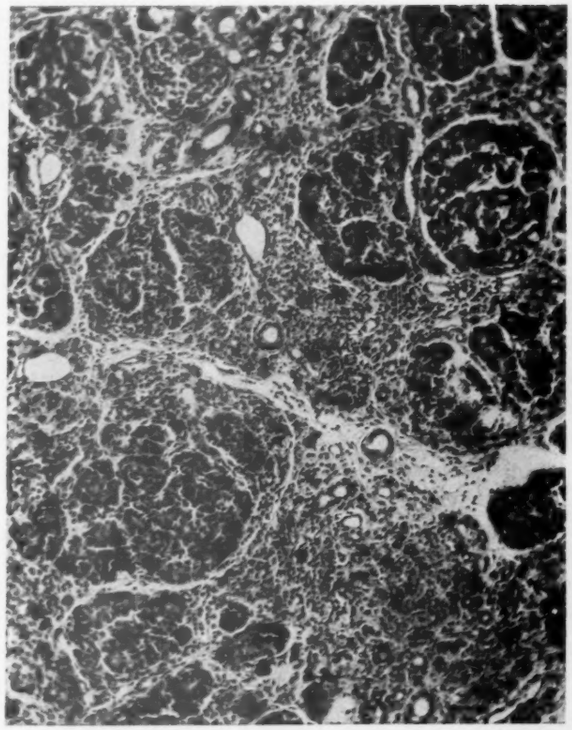

FIG. 3. Pancreas (May 11, 1956). There is fairly marked interacinar and interlobular fibrosis and degeneration and connective tissue proliferation. Hemosiderin is present in the acini and fibrous tissue. Atrophy of the islets of Langerhans was found in other sections. Prussian Blue stain.

with hemosiderin. Scattered throughout the spleen were areas of severe, patchy congestion. The liver (Fig. 2) displayed prominent fibrosis of the portal triads with fairly marked lymphocytic infiltration. Islets of hepatic regeneration were seen. The hepatic cord cells, the cells of the portal area, and the Kupffer cells all contained prominent amounts of hemosiderin. The normal architecture of the pancreas was lost (Fig. 3), with a prominent fibrous stromal reaction involving both the acini and the islets. Patchy areas contained appreciable quantities of hemosiderin. The adrenals contained a few foci of hemorrhage, and hemosiderin-containing cells were noted in abundance in the zona glomerulosa. Hemosiderin deposition was also observed in the myocardial fibers of the heart and in the mucosa of the gastrointestinal tract.

COMMENT

Approximately three years after undergoing a portacaval shunt for bleeding esophageal varices secondary to Laennec's cirrhosis both clinical and laboratory evidence of frank hemochromatosis developed. This latter condition was manifested by the onset of diabetes mellitus, slate grey skin, elevated serum iron and decreased unsaturated iron binding capacity. The autopsy findings confirmed the diagnosis. During the patient's first admission he received only enough whole blood to compensate his acute losses; thereafter, he received no transfusions. He did not present a picture resembling hemolytic anemia at any point in his illness. Furthermore, he was never given any supplemental iron either orally or parenterally; although it cannot be stated with certainty that he did not ingest iron on his own during this period.

Available evidence indicates that the total body content of iron in hemochromatosis ranges from 10 to 50 gm. [*2*] in contrast to the 4 to 5 gm. found in normal persons [*7*]. For a person to assimilate enough iron over a three-year period to reach these abnormal levels would require the absorbtion of at least 5 or 6 mg. of iron daily. Recent studies have shown that patients suffering from hemochromatosis may absorb from 20 to 80 per cent of an ingested dose of radioactive iron [*8–10*]. Since the normal intake of iron approximates 15 mg. a day, these

data suggest that such persons may indeed add 3 to 12 mg. of iron daily to their body stores.

Although this patient may have been accumulating excessive amounts of iron prior to surgery in December, 1952, the liver biopsy specimen showed only portal cirrhosis without evidence of any hemosiderin deposition. If large quantities of iron were present, they must have existed as ferritin, which cannot be demonstrated by existing staining technics. Since there is no evidence that ferritin *per se* can cause tissue damage, it is reasonable to assume that liver disease preceded the development of hemochromatosis. It is also evident that the patient must have absorbed appreciable quantities of iron in the three and a half years prior to his death.

The possible relationship between a portacaval shunt and the development of hemochromatosis is unknown. However, despite the large number of patients who have undergone this operation, such a complication has never been reported. Sheldon [*1*], Finch and Finch [*2*], and others [*3,5,6,11*] have noted the high incidence of cirrhosis in patients with hemochromatosis, but they have not studied patients before excessive iron storage occurred. Only the fortuitous circumstance of a surgical operation and liver biopsy and, three and a half years later, an autopsy permitted the observation in the aforementioned patient that cirrhosis preceded the development of hemochromatosis. Since it is known that iron metabolism may be abnormal in liver disease [*12–15*], it seems very possible that hemochromatosis developed in this patient as the result of preexisting cirrhosis, a viewpoint previously proposed by Knutsen [*16*]. However, the mechanism remains completely obscure. The high incidence of Laennec's cirrhosis as compared with the relatively infrequent occurrence of hemochromatosis is well known. Moreover, the iron content of the livers of some patients dying from postalcoholic cirrhosis has been shown to be significantly decreased when compared with normal livers [*17*].

SUMMARY

A patient with proved Laennec's cirrhosis without hemochromatosis is described in whom, three and a half years following a portacaval shunt for bleeding esophageal varices, frank hemochromatosis developed. No explanation for the rapid development of hemochromatosis is apparent.

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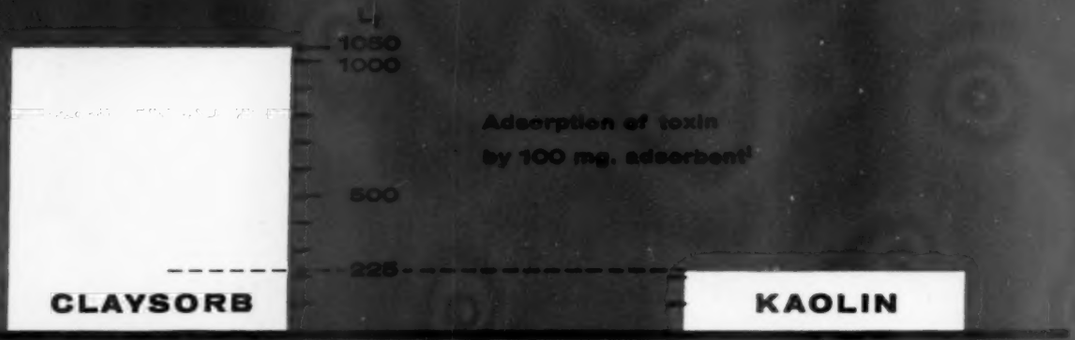

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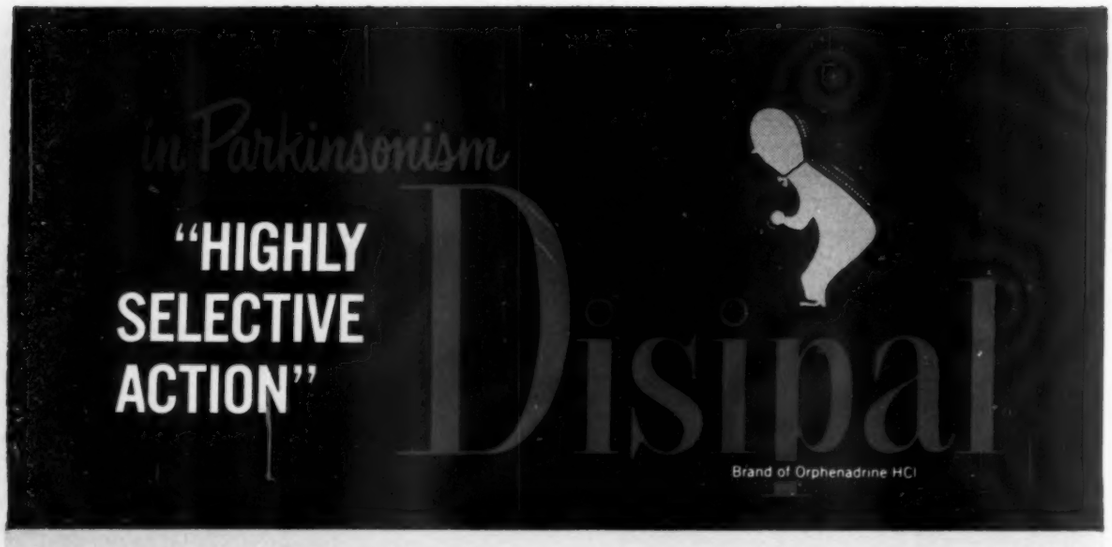

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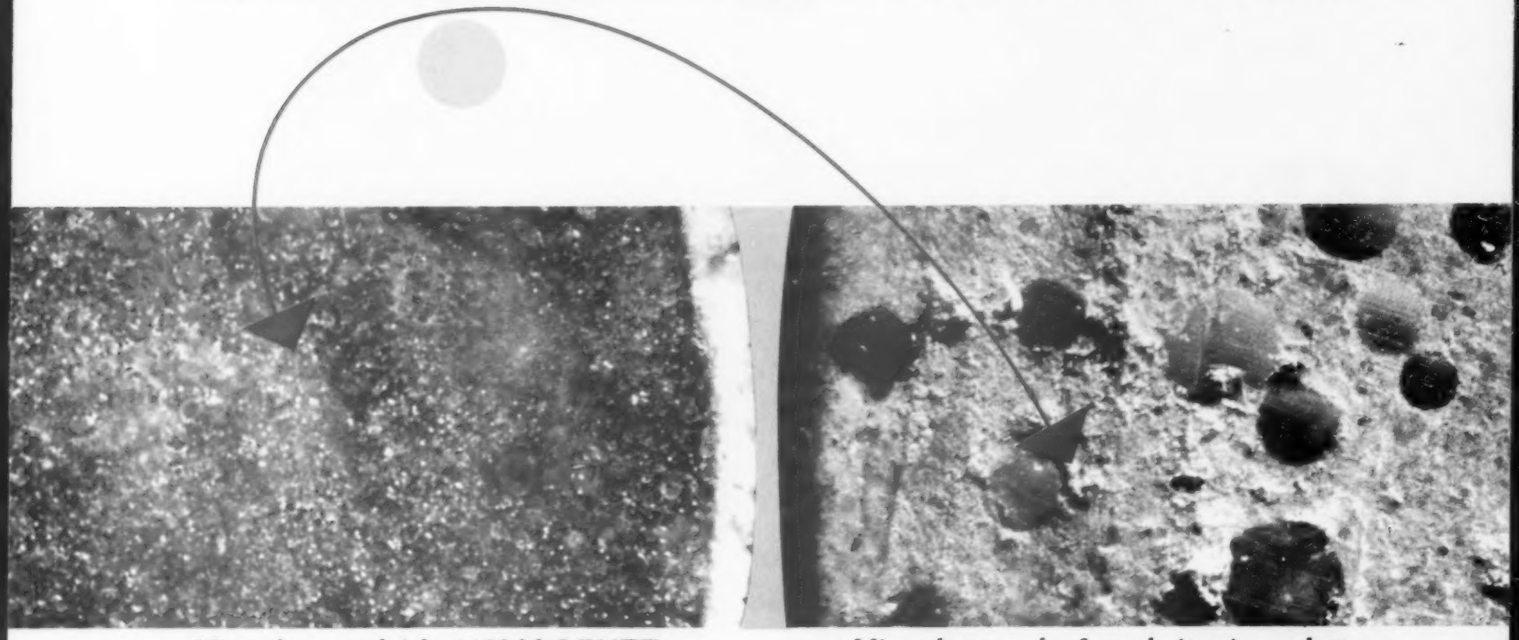

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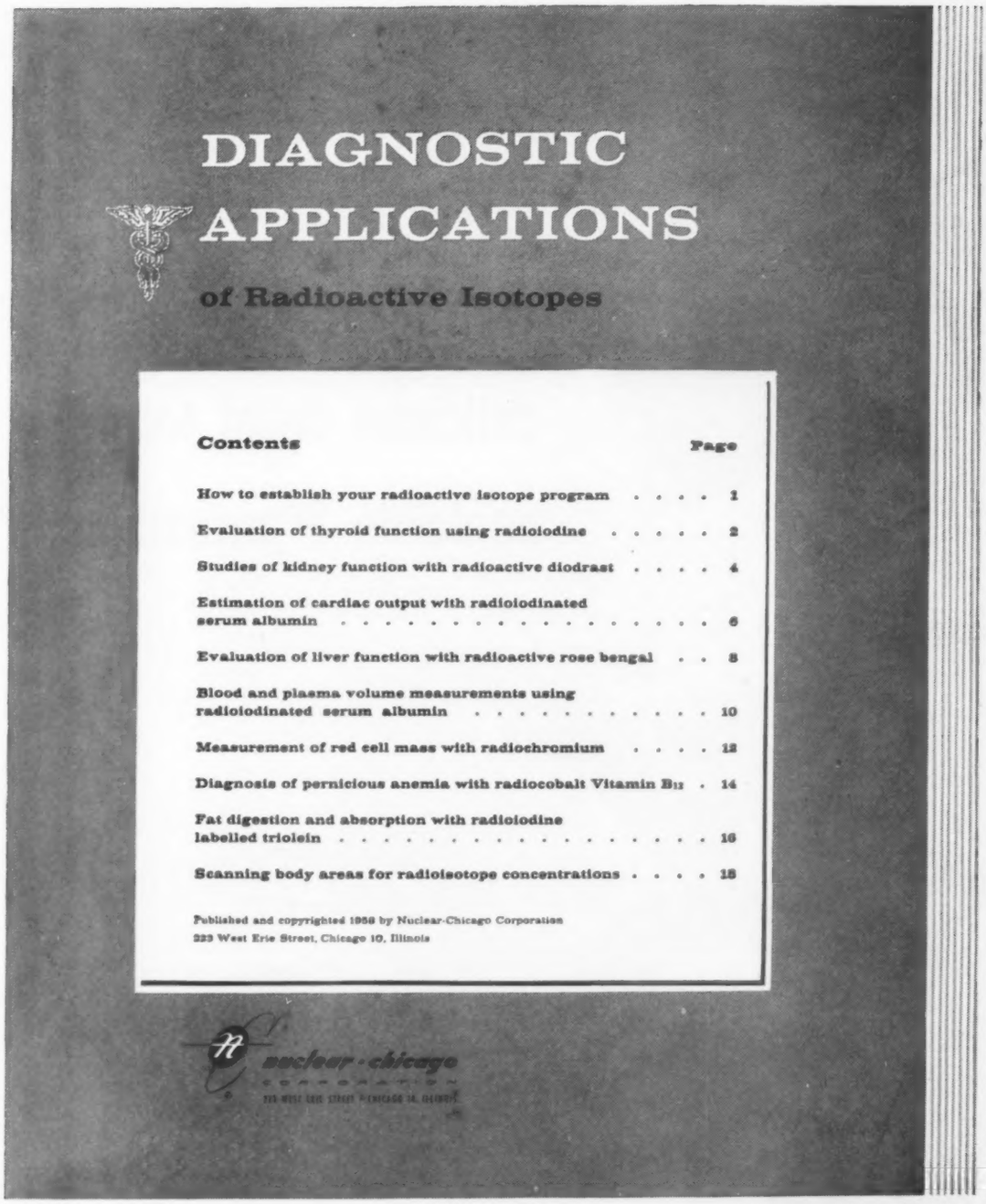
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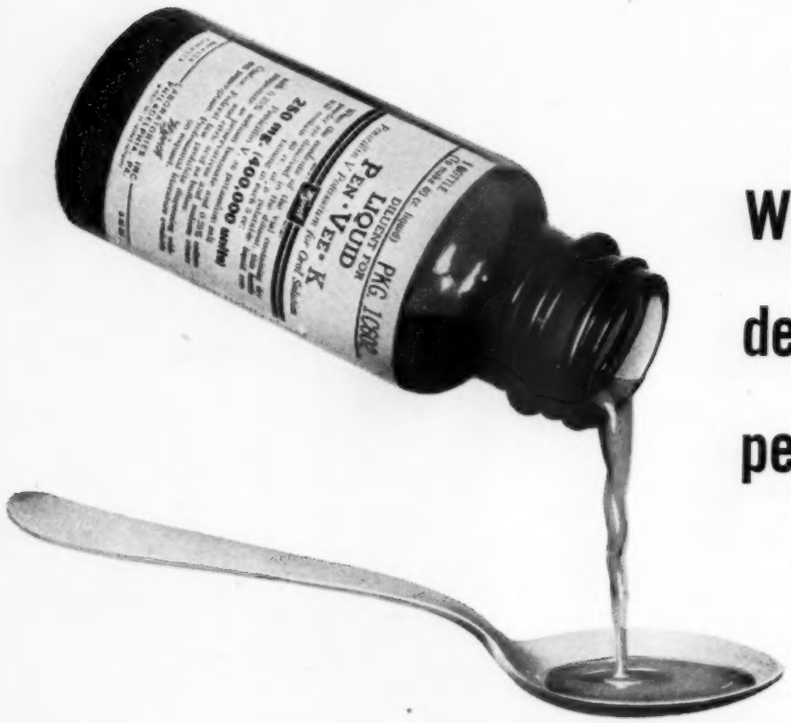

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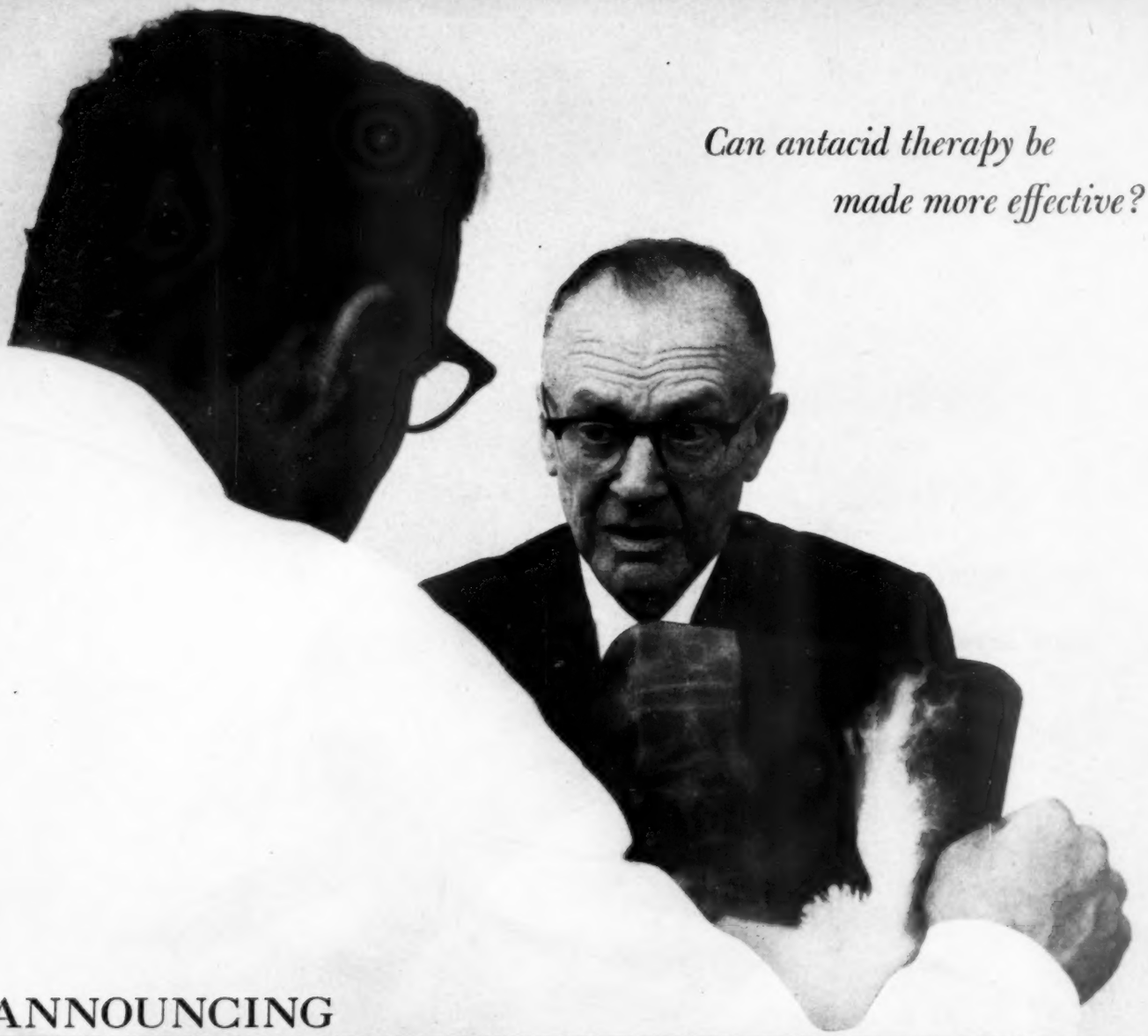

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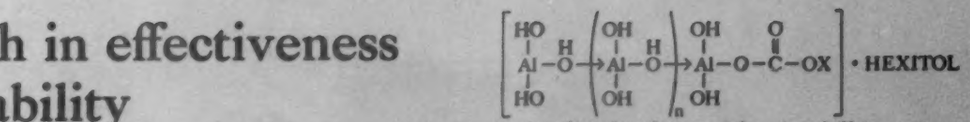

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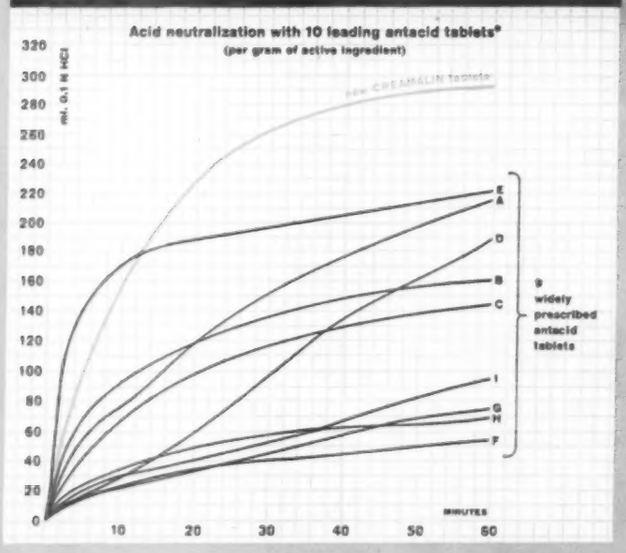

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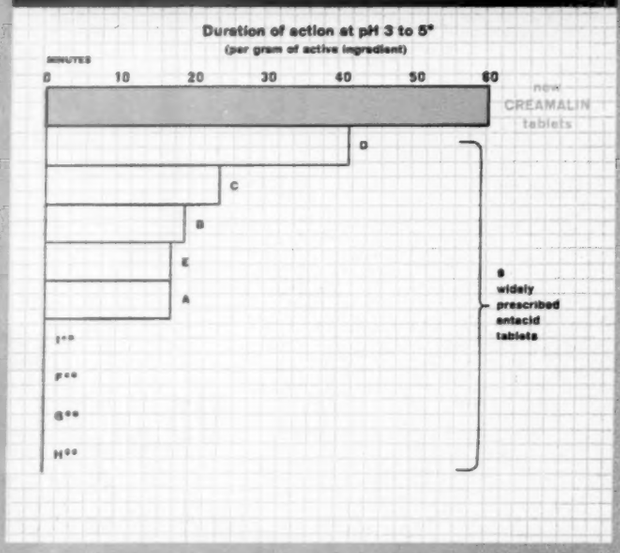

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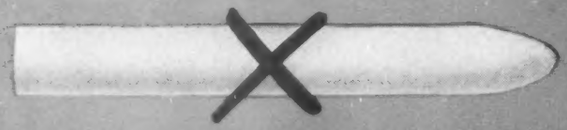

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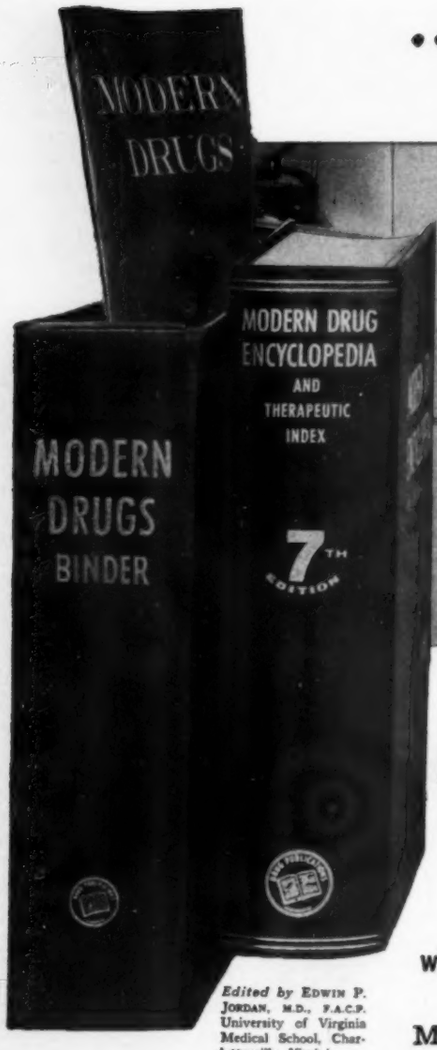

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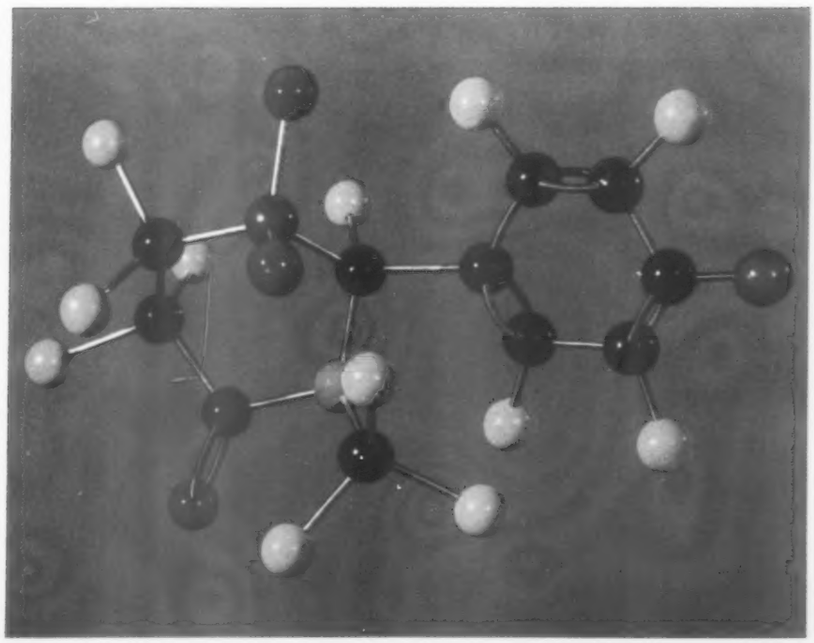

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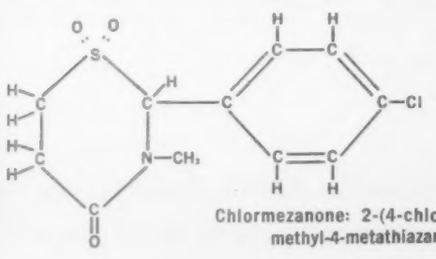

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Clinical studies of 4092 patients by 105 physicians[1] have demonstrated that Trancopal often is effective when other drugs have failed. From these studies it is evident that Trancopal can provide more help for a greater number of tense, spastic, and/or emotionally upset patients than can any other chemotherapeutic agent in current use.

In musculoskeletal conditions[1]

effective in **91%** of patients

INDICATIONS

- Low back pain (lumbago)
- Bursitis
- Osteoarthritis
- Fibrositis
- Myositis
- Postoperative myalgias
- Neck pain (torticollis)
- Rheumatoid arthritis
- Disk syndrome
- Joint disorders (ankle sprain, tennis elbow, etc.)

By relieving muscle spasm and pain, Trancopal permits early and active purposeful exercise and physical therapy to accomplish maximal benefits for rapid recovery.

Trancopal

Dosage: One Caplet (100 mg.) orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

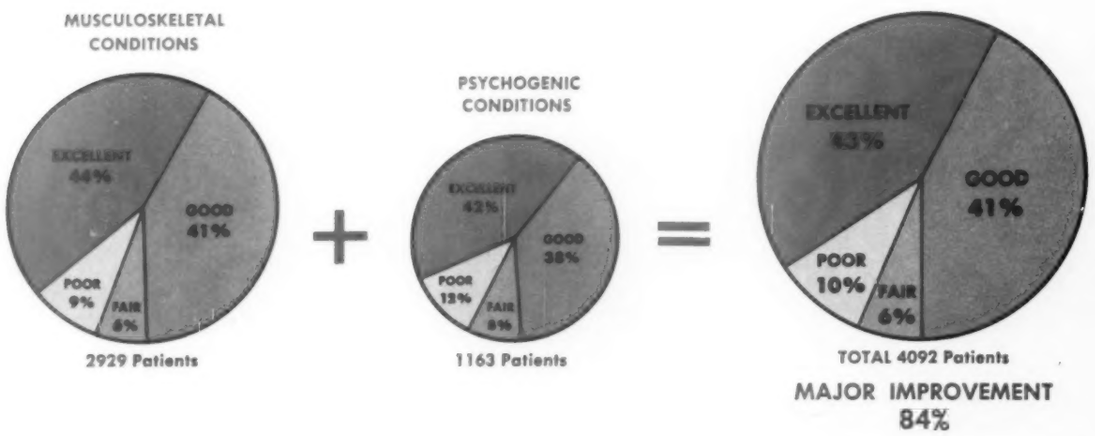
In anxiety and tension states[1]

effective in 88% of patients

INDICATIONS

Anxiety and tension states	Dysmenorrhea
Premenstrual tension	Asthma
Emphysema	Angina pectoris

Because of its exceptional calmative property, Trancopal "...allows the patient to use his energies in a more productive manner in overcoming his basic problem."[2]



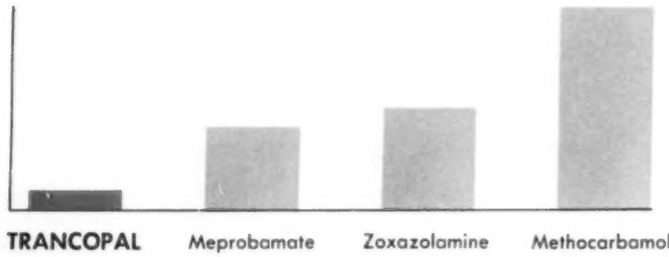
Of the total patients treated, Trancopal produced excellent results in 43 per cent, good results in 41 per cent, fair results in 6 per cent, and poor results in 10 per cent.

Better tolerated and safer than older drugs[3]

With Trancopal there is no clouding of consciousness, no euphoria or depression. Even in high dosage, there is no perceptible soporific effect. Because it does not irritate gastric mucosa, it can be taken without regard to mealtimes. Administration does not hamper work — or play. There are no known contraindications. Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage.
Toxicity is extremely low. And Trancopal has a lower incidence of side effects than has zoxazolamine, methocarbamol or meprobamate.

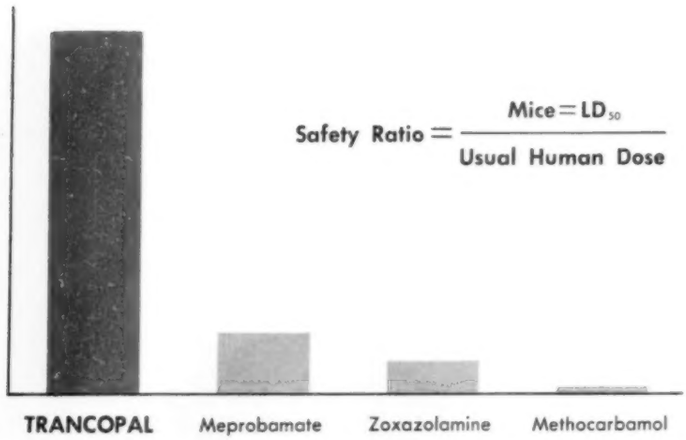
Comparison with 3 widely used central relaxants

When compared with three widely used central relaxants for activity, safety and clinical effectiveness, Trancopal offers definite desirable advantages.



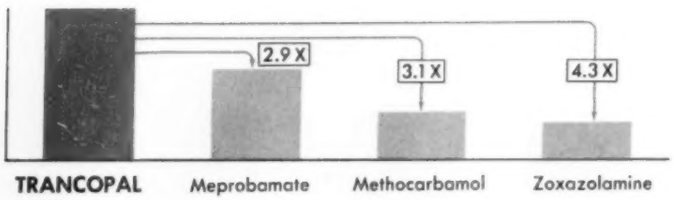
for activity

In the usual human dose, Trancopal is four to ten times as potent per milligram.



for safety

Comparative pharmacologic tests showed that Trancopal is up to thirteen times as safe or up to thirteen times less toxic. The measure of safety was the LD_{50} in mice/usual human dose.



for clinical effectiveness

A clinical comparison in low back pain, torticollis, bursitis and anxiety states showed that Trancopal is up to four times as effective. Each of the 40 patients received all four drugs in random rotation for several days. Although each of the four gave some relief, only the one providing the most effective relief was recorded.

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References: 1. Cooperative Study, Department of Medical Research, Winthrop Laboratories. • 2. Gans, S.E.: To be published. • 3. Lichtman, A.L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958.

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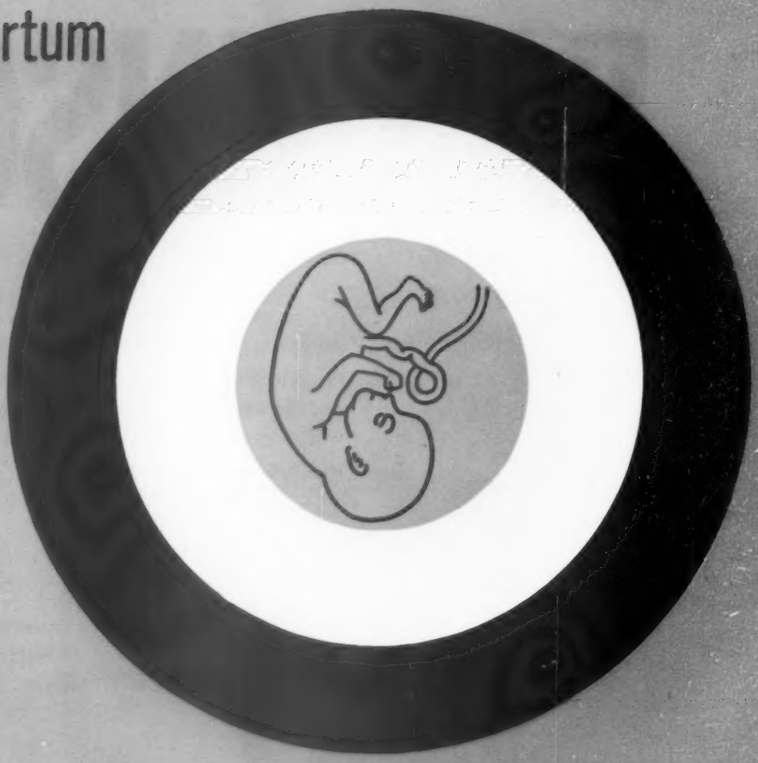

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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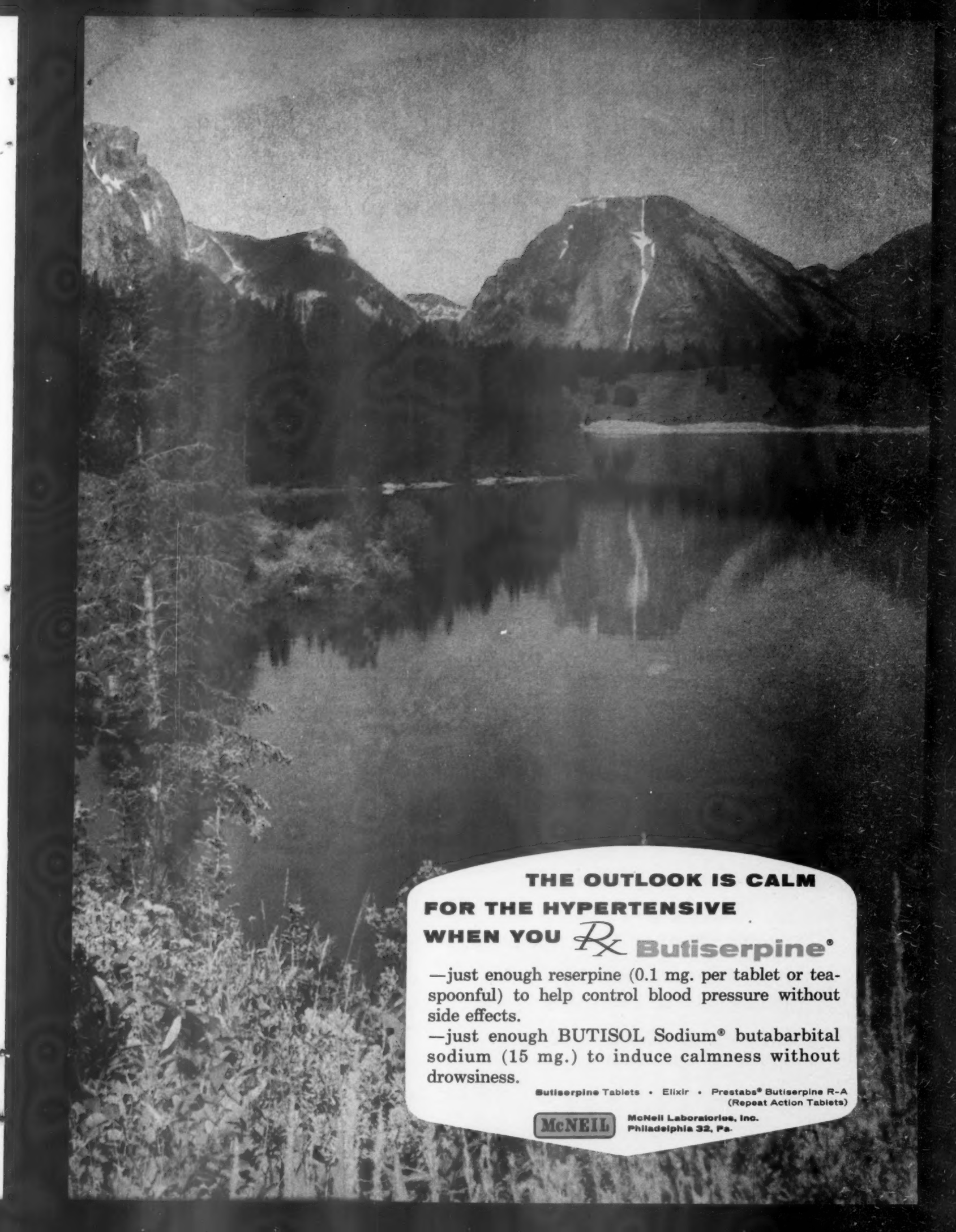
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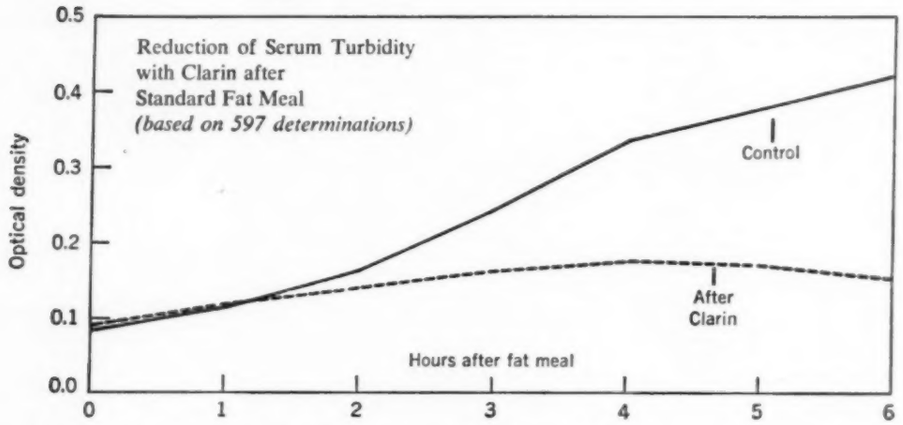

Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood,[1,2] but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

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1. Council on Drugs, J.A.M.A. *166*:52 (Jan. 4) 1958. 2. Hahn, P. F.: Science *98*:19 (July 2) 1943. 3. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. 4. Rubio, F. A., Jr.: Personal communication. 5. Engelberg, H., *et al.*: Circulation *13*:489 (April) 1956.

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REFERENCES: **1.** Cotten, H. B., Herren, W. S., McAdory, W. C., and Klapper, M. S.: Am. J. M. Sc. *230*:408 (Oct.) 1955. **2.** Schneider, J. A.: Am. J. Physiol. *181*:64 (April) 1955. **3.** Schumann, H.: Ztschr. Kreislaufforsch. *43*:614 (May) 1954. **4.** Schumann, H.: Klin. Wchnschr. *33*:124 (Feb.) 1955. **5.** Schumann, H.: Ztschr. Kreislaufforsch. *45*:115 (Feb.) 1956. **6.** Halprin, H.: J. M. Soc. New Jersey *52*:616 (Dec.) 1955. **7.** Hollister, L. E.: Personal communication 1956. **8.** Achor, R. W. P., Hanson, N. O., and Gifford, R. W., Jr.: J.A.M.A. *159*:841 (Oct. 29) 1955. **9.** Harris, R.: Ann. New York Acad. Sc. *59*:95 (April 30) 1954. **10.** Schumann, H.: Ztschr. Kreislaufforsch. *43*:614 (May) 1954. **11.** Hughes, W., Dennis, E., McConn, R., Ford, R., and Moyer, J. H.: Am. J. M. Sc. *228*:21 (July) 1954. **12.** Wiggers, C. J.: *Physiology in Health and Disease*, 5th Ed., Lea & Febiger, Philadelphia, 1949, p. 328. **13.** Zaky, H. A.: Lancet *2*:600 (Sept. 18) 1954. **14.** Perera, G. A.: J.A.M.A. *159*:439 (Oct. 1) 1955. **15.** Avol, M., and Vogel, P. J.: J.A.M.A. *159*:1516 (Dec. 17) 1955.

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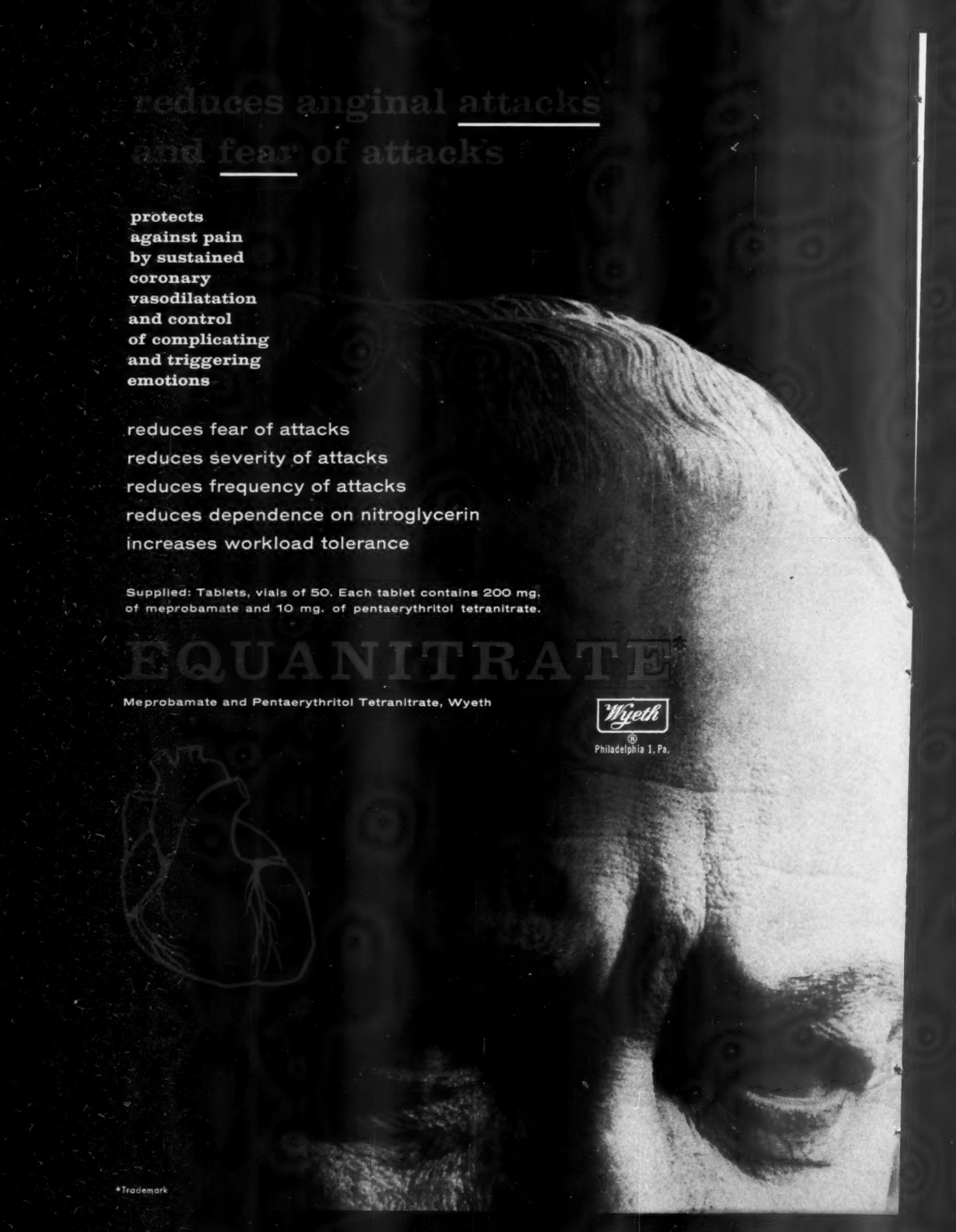
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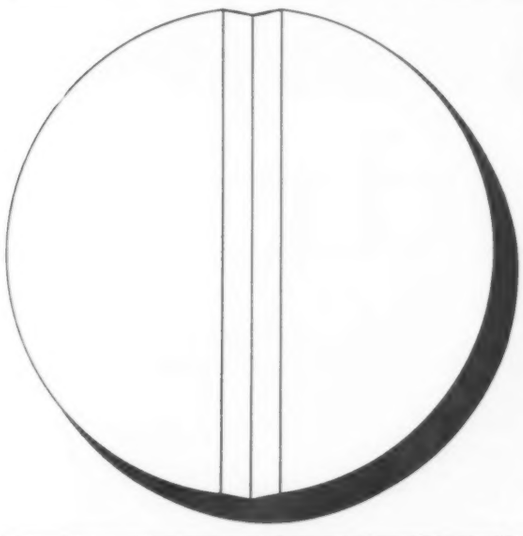

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Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—ranging from **mild to moderately severe**—due to **hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever**

Clinical effectiveness confirmed by millions of cases
Specific in many common infections
Daily dosage may be spaced without regard to mealtime
Ease of administration with oral penicillin
Economy for the patient

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new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

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PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

now...when treating upper

Madribon

Disease	No. of Patients	Response: Good or Excellent	Response: Poor
Otitis media	72	65	7
Bronchitis	11	10	1
Obstructive laryngotracheitis	3	3	0
Tonsillitis	21	18	3
Cervical adenitis	13	13	0
Purulent rhinitis or sinusitis	19	16	3
Total	139	125	14

From a study by E. H. Townsend and A. Borgstedt[1]

safe "No side reactions to sulfadimethoxine were observed in the entire series of 167 patients."[1] **effective** "Remarkable improvement, characterized by subjective relief and disappearance of inflammatory symptoms, occurred in 107 out of the 111 patients under study."[2] **economical** "In addition to the clinical efficiency attributable to sulfadimethoxine . . . the economy involved in medication with a fast-acting chemotherapeutic agent warrants its early use. . . ."[3]

respiratory infections

The fastest growing antibacterial bibliography:

1. E. H. Townsend and A. Borgstedt, *Antibiotics Annual 1958-1959*, in press. **2.** J. C. Elia, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **3.** B. H. Leming, Jr., C. Flanigan, Jr. and B. R. Jennings, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **4.** H. P. Ironson and C. Patel, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **5.** S. Ross, J. R. Puig and E. A. Zaremba, *Antibiotics Annual 1958-1959*, in press. **6.** J. D. Young, Jr., W. S. Kiser and O. C. Beyer, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **7.** T. D. Michael, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **8.** W. A. Leff, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **9.** B. A. Koechlin, W. Kern and R. Engelberg, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **10.** R. J. Schnitzer and W. F. DeLorenzo, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **11.** R. J. Schnitzer, W. F. DeLorenzo, E. Grunberg and R. Russomanno, *Proc. Soc. Exper. Biol. & Med.*, *99*:421, 1958. **12.** W. F. DeLorenzo and R. Russomanno, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **13.** B. Fust and E. Boehni, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **14.** W. F. DeLorenzo and A. M. Schumacher, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959. **15.** W. P. Boger, *Antibiotics Annual 1958-1959*, in press. **16.** O. Brandman, C. Oyer and R. Engelberg, *J. M. Soc. New Jersey*, *56*:24, Jan. 1959. **17.** J. F. Glenn, J. R. Johnson and J. H. Semans, *Antibiotic Med. & Clin. Therapy*, *6*:(Suppl. 1), 1959.

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so versatile you can give it intramuscularly

intravenously

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CHLOROMYCETIN SUCCINATE is a soluble ester of CHLOROMYCETIN that can be administered intramuscularly, intravenously, or subcutaneously. Highly soluble in water or other aqueous parenteral fluids, CHLOROMYCETIN SUCCINATE solution is easily prepared for use by recommended parenteral routes in a wide range of concentrations. Tissue reaction at the site of injection is minimal,[2] permitting continuous daily dosage, even in pediatric patients.[1]

RAPID, EFFECTIVE BLOOD LEVELS

CHLOROMYCETIN SUCCINATE is rapidly hydrolyzed by body esterases and produces effective blood and tissue concentrations of CHLOROMYCETIN within a short time.[2] Although the intravenous route provides high immediate serum concentrations, after four hours the blood levels of CHLOROMYCETIN for all three routes are about equal, and effective concentrations are maintained for eight hours.[3]

WIDE-SPECTRUM ANTIMICROBIAL EFFECTIVENESS

CHLOROMYCETIN SUCCINATE providing broad-spectrum antimicrobial effectiveness, may be used whenever CHLOROMYCETIN is indicated. It has produced effective response in respiratory, gastrointestinal, and rickettsial infections.[1,4,5] Because of the rapid, effective blood levels of CHLOROMYCETIN provided, it is especially useful in *Hemophilus influenzae* meningitis, in certain septicemias, typhoid fever, and other *Salmonella* infections.[1,5]

TYPICAL CLINICAL EXPERIENCE WITH CHLOROMYCETIN SUCCINATE

Type of infection	Number of Patients	RESULTS Excellent to Good	Fair	Poor
Respiratory[1,4]*	32	32		
Shigella dysentery[1]	14	14		
Enteritis[1]	10	6	2	2
Bacteremia[1,5]	5	5		
Meningitis[1,5]	4	3		1**
Rocky Mountain spotted fever[1,5]	2	2		
Ear abscess with cellulitis[4]	1	1		
Lung abscess[4]	1			1
Typhoid fever[5]	1	1		
TOTALS	70	64	2	4

*Includes 15 patients who were administered CHLOROMYCETIN SUCCINATE by nebulization under intermittent positive pressure breathing.

**Patient was hydrocephalic at birth; cerebrospinal fluid was sterile at time of death.

WELL TOLERATED

CHLOROMYCETIN SUCCINATE is well tolerated, even by small children. Signs of irritation at injection sites have been few.[1-5] Its relative freedom from irritation makes it possible to use CHLOROMYCETIN SUCCINATE for prolonged periods in patients who are not able to take oral medication.

DOSAGE AND ADMINISTRATION—*Adults:* 1 Gm. every six to eight hours. *Children:* 100 mg. per Kg. of body weight per day in divided doses at six- to eight-hour intervals. The total dose in children should not exceed the adult dose of 1 Gm. given at any single injection, with exception of treatment of *Hemophilus influenzae* meningitis in which higher doses are employed.

In all cases, severity of infection and clinical response to therapy should be the guiding factors determining the proper dosage schedule.

Premature and full-term newborn infants require special dosage supervision. For details see literature.

SUPPLY—CHLOROMYCETIN SUCCINATE (chloramphenicol sodium succinate, Parke-Davis) is supplied in Steri-Vials,® each containing the equivalent of 1 Gm. chloramphenicol; packages of 10.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately, or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES—(1) Ross, S.; Puig, J. R., & Zaremba, E. A., in Welch, H., & Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 803. (2) Glazko, A. J., *et al.*: *ibid.*, p. 792. (3) Unpublished data: Research Laboratories, Parke, Davis & Company, 1958. (4) Payne, H. M., & Hackney, R. L., Jr., in Welch, H., & Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 821. (5) McCrumb, F. R., Jr.; Snyder, M. J., & Hicken, W. J.: *ibid.*, p. 837.

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MEDICAMENTA VERA

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- postoperatively
- in pregnancy when vomiting is persistent
- following neurosurgical diagnostic procedures
- in infections, intra-abdominal disease, and carcinomatosis
- after nitrogen mustard therapy

for nausea and vomiting

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Squibb Trifluprom azine

- provides prompt, potent, and long-lasting control
- capable of depressing the gag reflex
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- may be given intravenously, intramuscularly and orally
- no pain or irritation on injection

ANTIEMETIC DOSAGE:
Intravenous: 8 mg. average single dose
Dosage range 2-10 mg.
Intramuscular: 15 mg. average single dose
Dosage range 5-15 mg.
If subsequent parenteral dose is needed, one-half the original dose will usually suffice
Oral: 10-20 mg. initially; then 10 mg. t.i.d.

SUPPLY:
Parenteral solution – 1 cc. ampuls (20 mg./cc.), 1 cc. multiple dose vials (20 mg./cc.)
Oral tablets – 10 mg., 25 mg., 50 mg., in bottles of 50 and 500

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"VESPRIN" ® IS A SQUIBB TRADEMARK

A workhorse "mycin" for common infections

respiratory infections

prompt, high blood levels

consistently reliable and reproducible blood levels

minimal adverse reactions

With well-tolerated CYCLAMYCIN, you will find it possible to control many common infections rapidly and to do so with remarkable freedom from untoward reactions. CYCLAMYCIN is indicated in numerous bacterial invasions of the respiratory system—lobar pneumonia, bronchopneumonia, tracheitis, bronchitis, and other acute infections. It has been proved effective against a wide range of organisms, such as pneumococci, H. influenzae, streptococci, and many strains of staphylococci, including some resistant to other "mycins." Supplied as Capsules, 125 and 250 mg., vials of 36; Oral Suspension, 125 mg. per 5-cc. teaspoonful, bottles of 2 fl. oz.

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1. McKenna, C. J.: Am. Pract. & Digest Treat. 6:417, 1955. 2. Moyer, J. H.: M. Clin. North America, March, 1957, p. 405.

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12.5 mg. per 5 cc.

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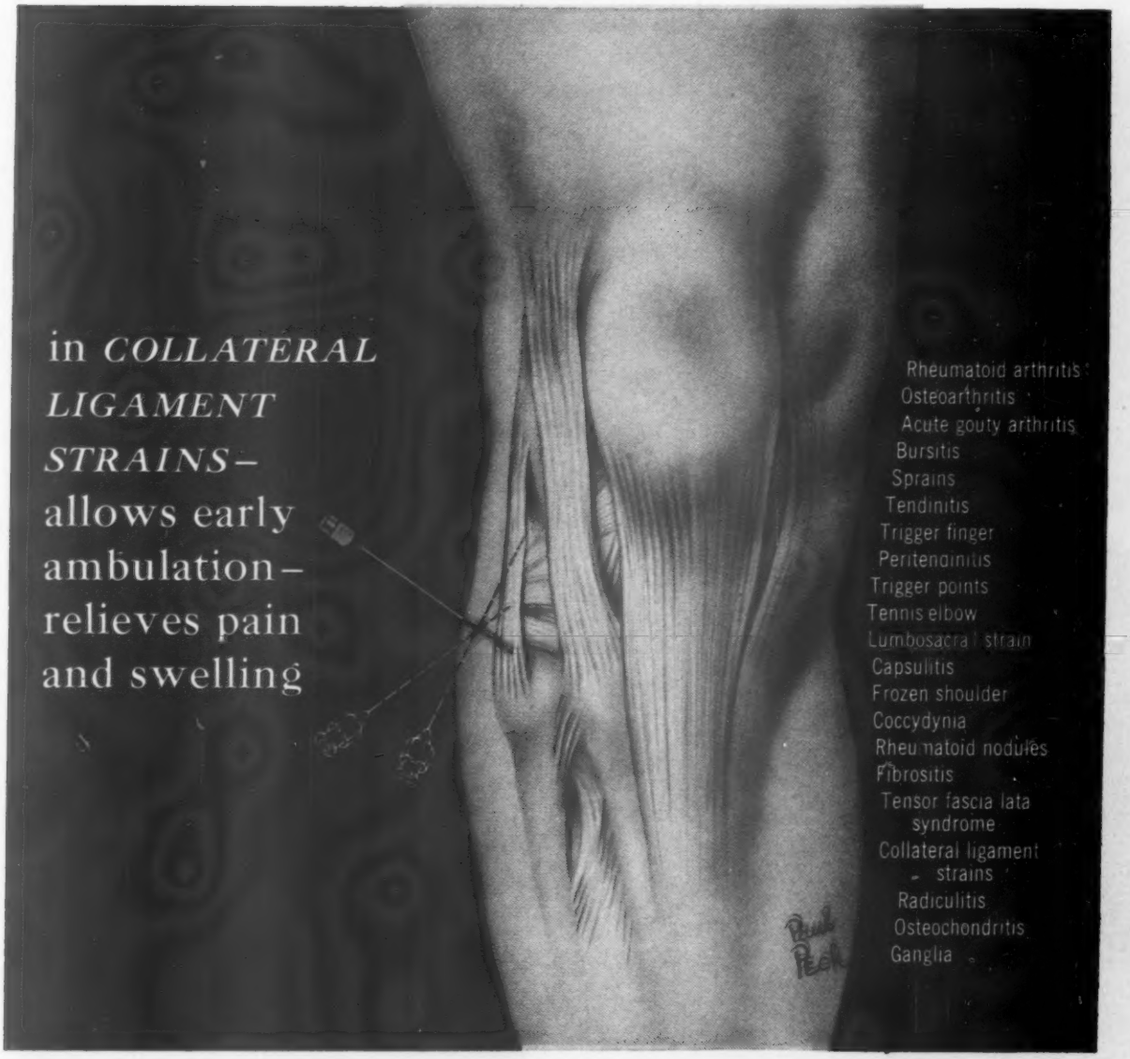
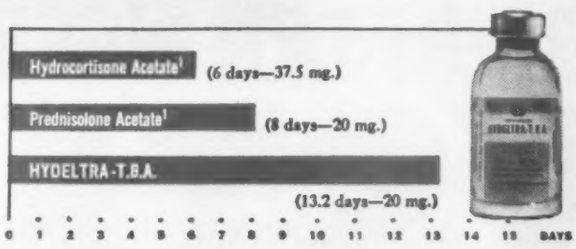
(Prednisolone *tertiary*-butylacetate, Merck)

for relief that lasts—longer



Duration of relief exceeds that provided by any other steroid ester


Hydrocortisone Acetate[1]
(6 days—37.5 mg.)
Prednisolone Acetate[1]
(8 days—20 mg.)
HYDELTRA-T.B.A.
(13.2 days—20 mg.)
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Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

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References: 1. Cronk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia Inc. 1958, p. 397 • 2. Newcomer, V. D.; Wright, E. T., and Sternberg, T. H.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia Inc., 1955, p. 686.

'MYSTECLIN'®, 'SUMYCIN'®, AND 'MYCOSTATIN'® ARE SQUIBB TRADEMARKS

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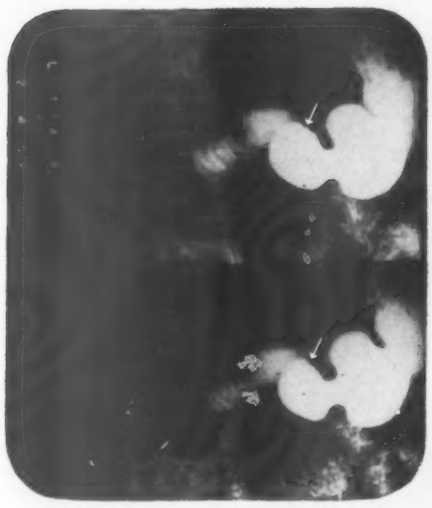
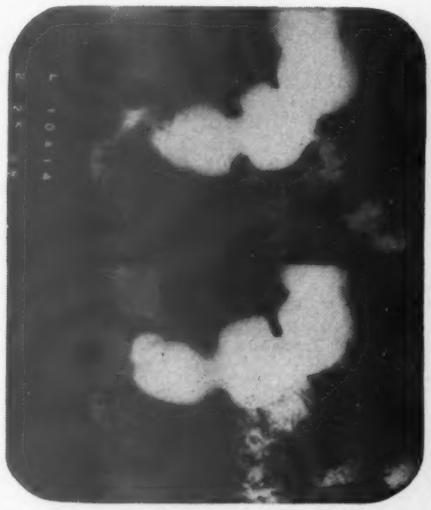
relieve the tension

—and control its G.I. sequelae



Patient A.S., age 53.
Intermittent crises of severe pain over 2 year period; hospital management with Sippy regimen provided relief of symptoms; however, symptoms recurred after each sojourn.



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PATHIBAMATE combines Meprobamate (400 mg.)—the noted tranquilizer-muscle relaxant widely accepted for management of tension and anxiety states—and PATHILON (25 mg.)—an extremely well-tolerated anticholinergic, long noted for prompt symptomatic relief based on peripheral atropine-like action with few side effects.

Indications:
Duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility.

Supplied:
Bottles of 100 and 1,000. Each tablet (yellow, ½-scored) contains Meprobamate, 400 mg.; PATHILON Tridihexethyl Chloride, 25 mg.

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1 tablet three times a day at mealtimes and 2 tablets at bedtime. Adjust dosage to patient response. Contraindicated in glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Also Available: PATHILON in four forms — ***Tablets*** of 25 mg., plain (pink) or with *phenobarbital,* 15 mg. (blue);
Parenteral — 10 mg./cc. — 1 cc. ampuls;
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*PATHILON is now offered as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could interfere with the results of certain thyroid function tests.

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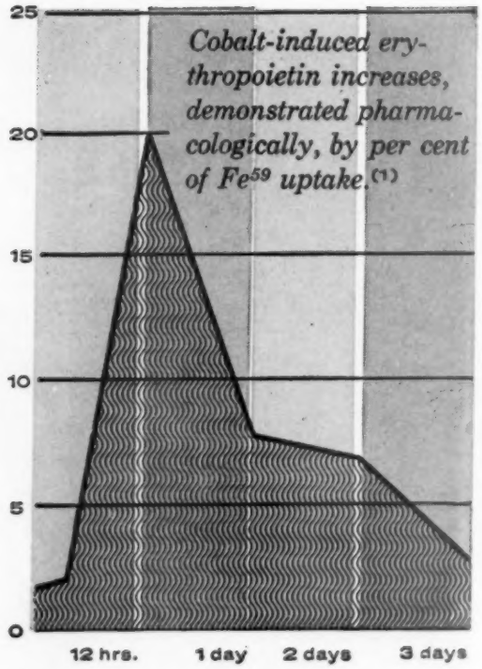

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Activates the physiologic mechanism in anemia therapy

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Only cobalt among therapeutic agents enhances production of erythropoietin to promote red cell formation.[1,2,3]

With Roncovite-MF, increased erythropoietin production permits excellent hematopoietic response with sharply reduced iron dosage.

Cobalt-iron (Roncovite therapy) has been demonstrated as superior to iron alone in the common hypochromic anemias such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy and refractory anemias of chronic infection.[4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: Blood 13:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O. and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C. and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. 1:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. 113:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas State J. Med. 51:686 (Oct.) 1955.

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tablets • alka capsules

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Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[2] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[2]

References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

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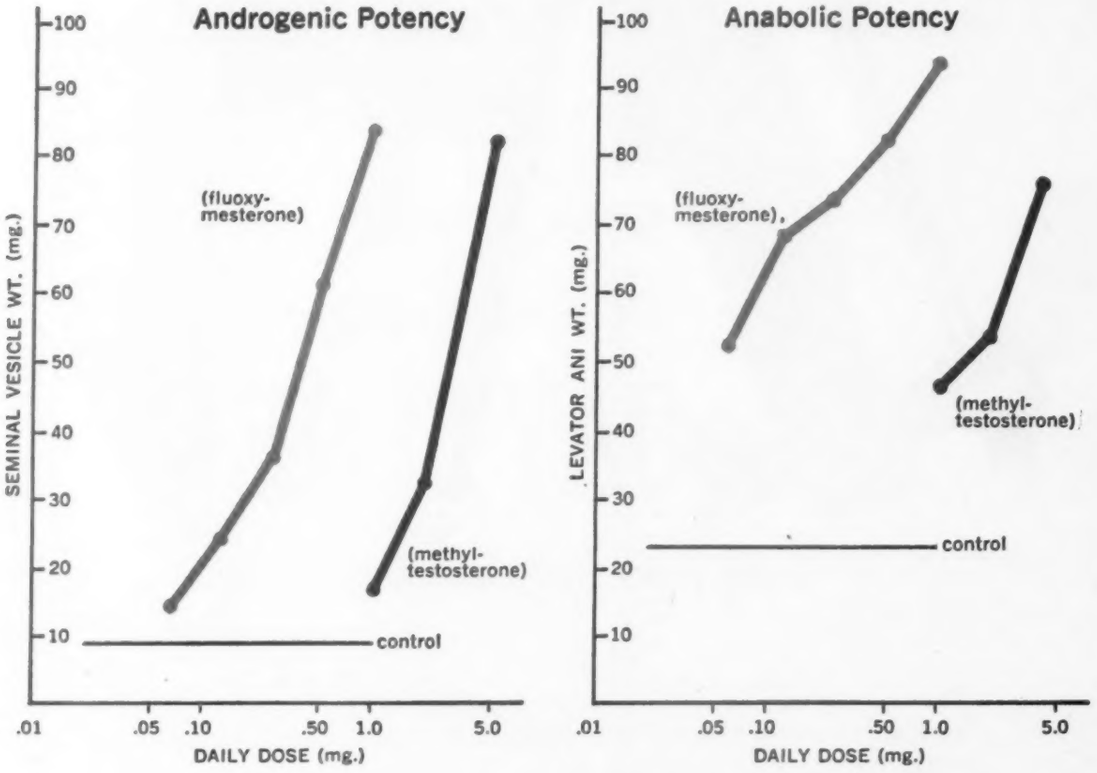
*Charts adapted from Lyster, S. C., Lund, G. H., and Stafford, R. O.: Endocrinology *58*:781 (June) 1956.



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Ultandren permits easily controlled administration of androgen therapy—without painful injections, local reactions or skipped doses. Weight for weight, it has an even greater therapeutic potency than parenterally administered testosterone derivatives, and at least five times the androgenic and anabolic activity of methyltestosterone tablets. Moreover, Ultandren does not increase undesirable effects such as virilism in females, and in therapeutic doses it induces little or no sodium and water retention. Jaundice, occasionally encountered with usual androgen therapy, has not been reported.

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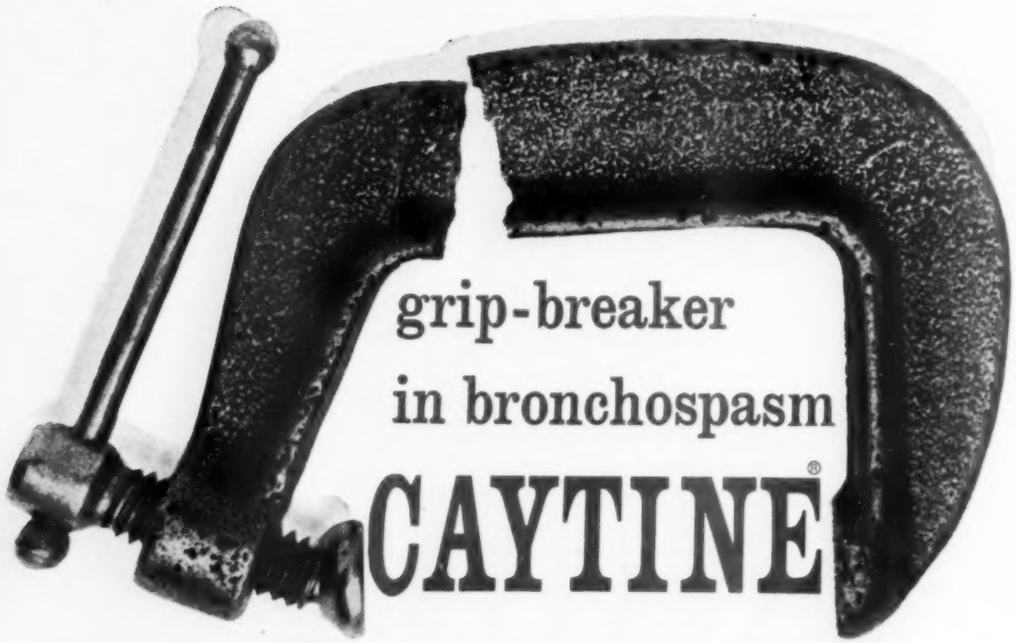

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orally, parenterally, and by inhalation

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three forms for individualized management: In patients with asthma, emphysema, bronchitis, bronchiectasis, CAYTINE Tablets, Inhalation, and Injection permit the physician to determine the treatment that gives the greatest relief with fewest side effects. CAYTINE increases vital capacity more than isoproterenol.[1] In geriatric patients, CAYTINE "...was more effective than any previous medication used."[2] There are a few side effects, but no toxic reactions, with the use of CAYTINE. No elevation of blood pressure, no adverse ECG, EEG, hepatic, renal or hematologic changes have been noted. Patients may experience palpitations and anxiety and should be so warned.

(1) Leslie, A., and Simmons, D. H.: Am. J. M. Sc. *234*:321, 1957. (2) Settel, E.: Am. Pract. & Digest Treat. *8*:1249, 1957.

For additional information request Brochure No. NDA 18, CAYTINE, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

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- *difficult-to-pass stools*
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  inadequate peristalsis
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- *or a combination of these symptoms*

for soft, easy-to-pass stools

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1. Mullnos, M. G., and Jerzy Glass, G. B.: Gastroenterology 24: 383-393 (May-Aug.) 1953.

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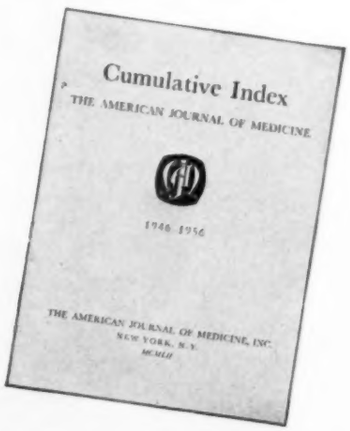

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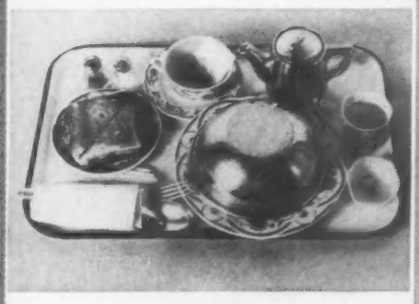

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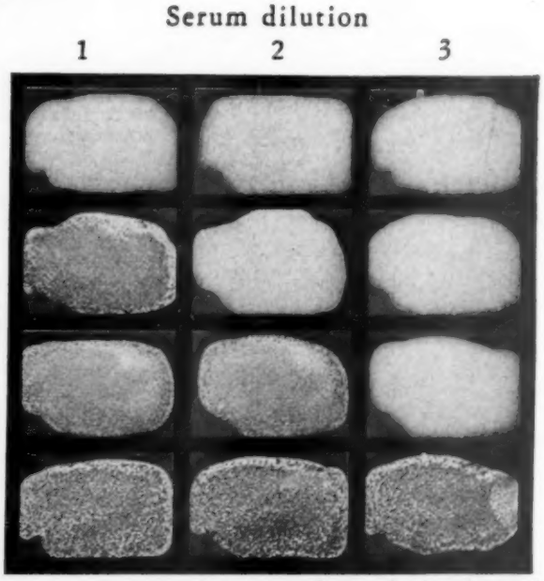

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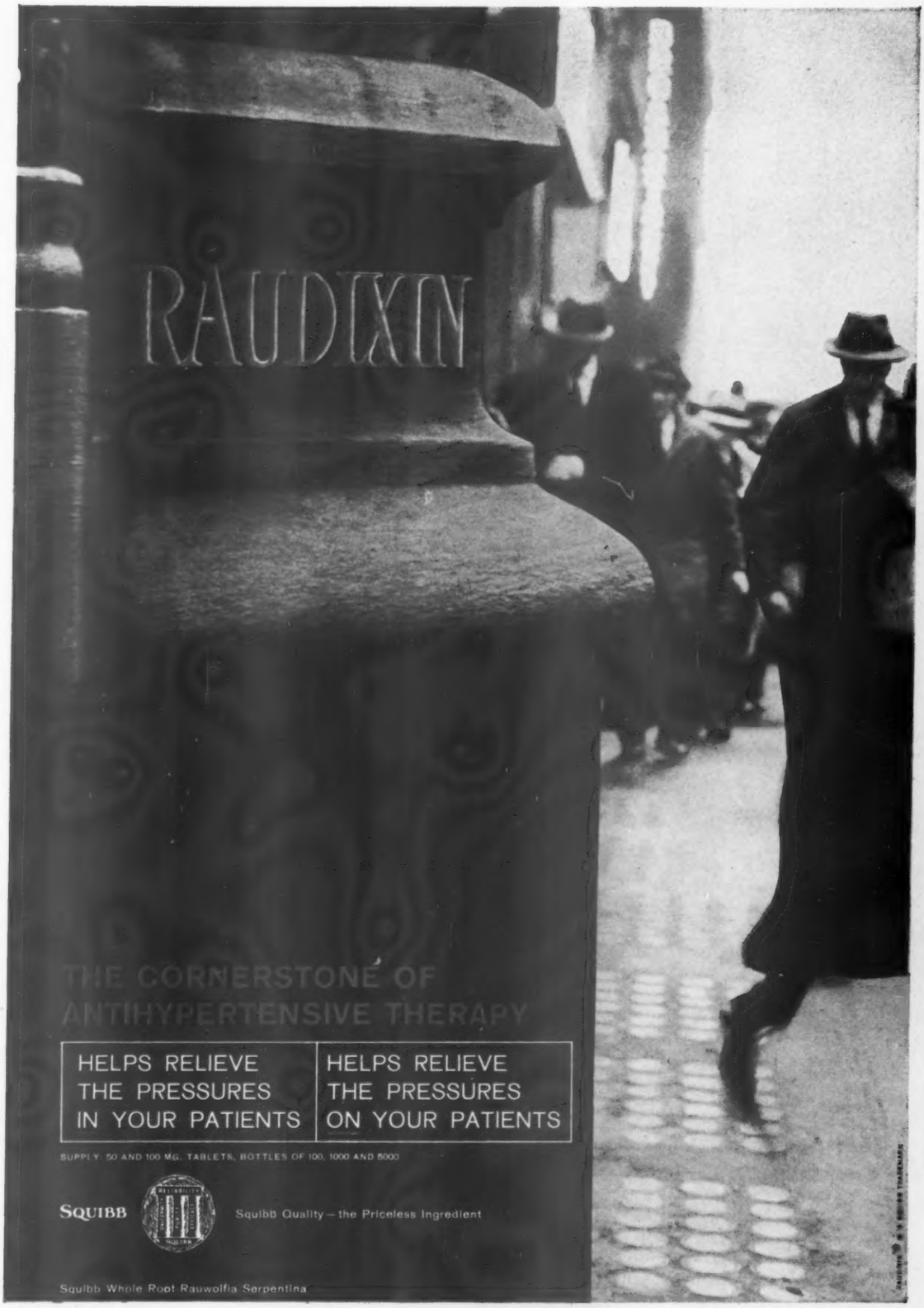
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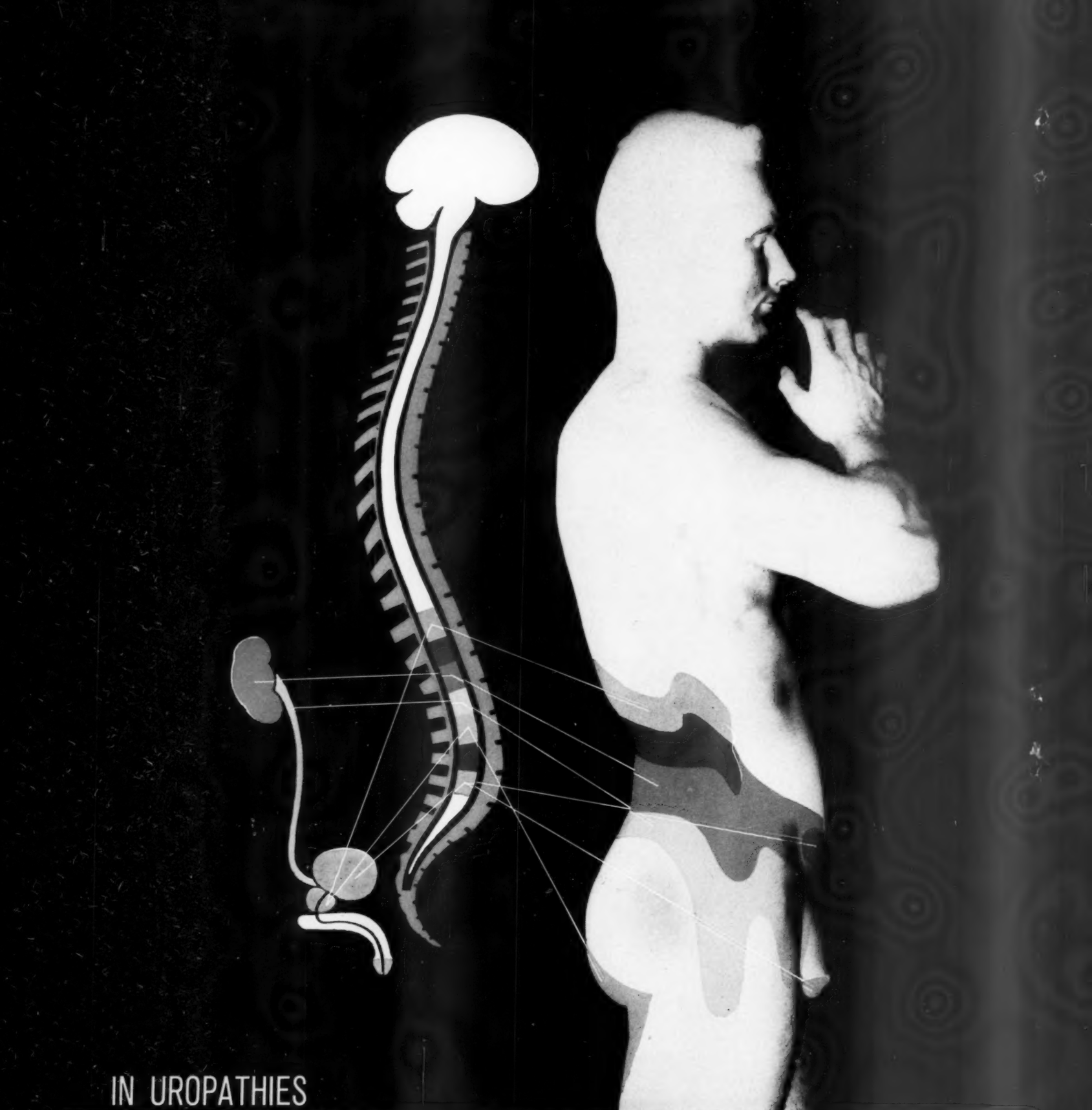

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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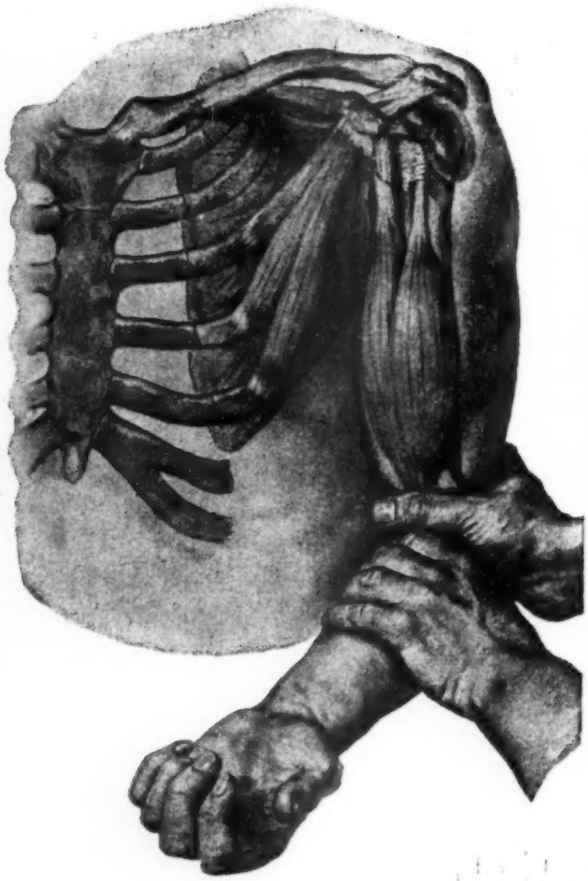

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1. Frankel, C. J., and Strider, D. V.: Presented at Meeting of American Academy of Orthopaedic Surgeons, New York, N. Y., Feb. 3, 1958.

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